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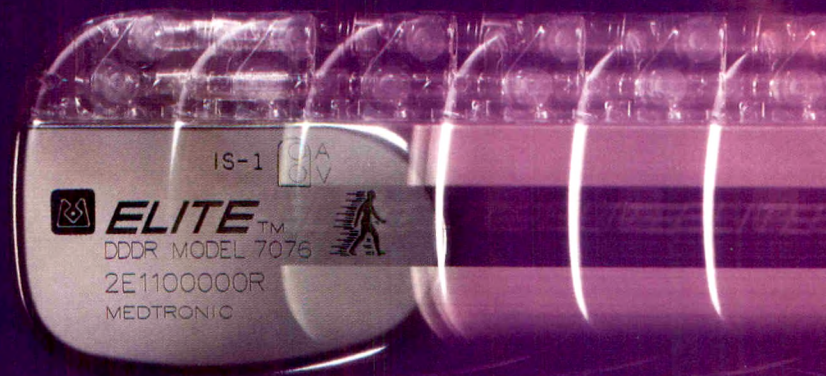
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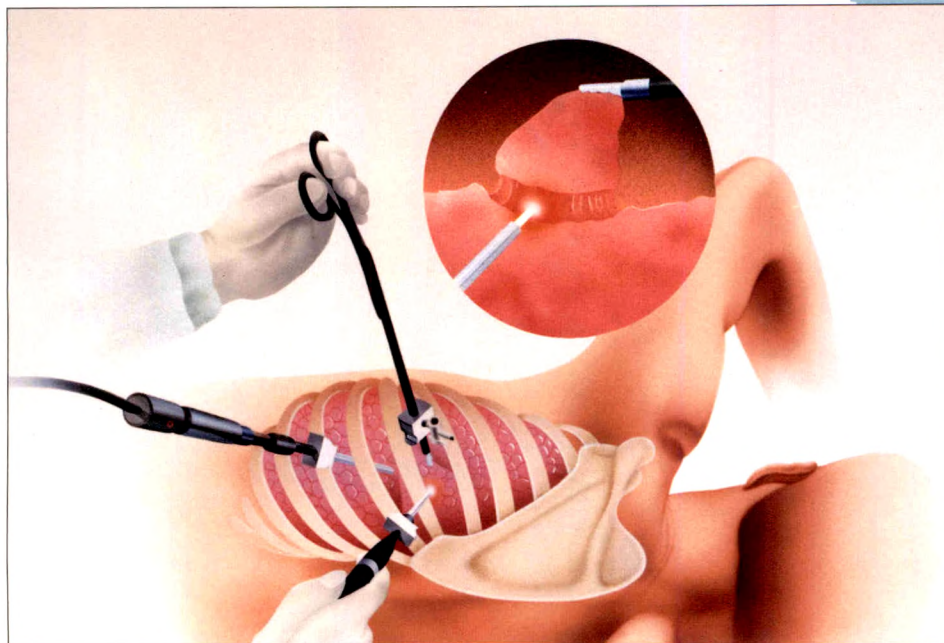
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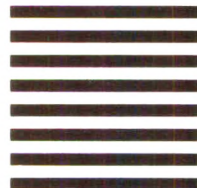
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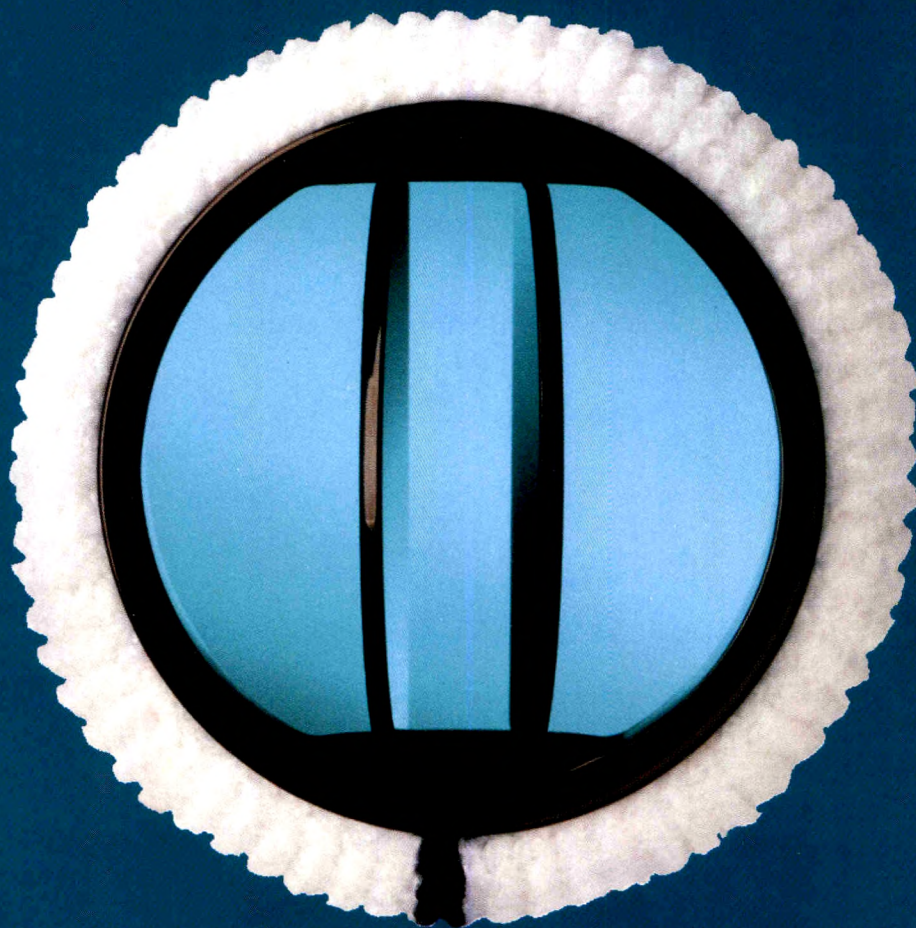


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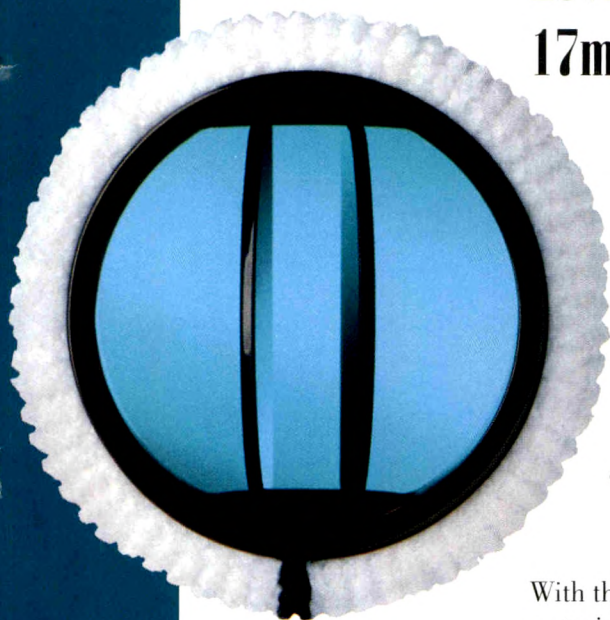
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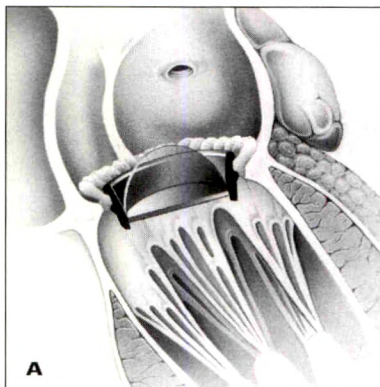
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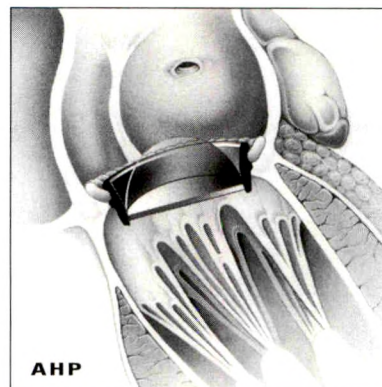
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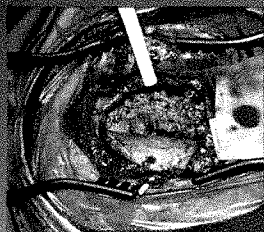
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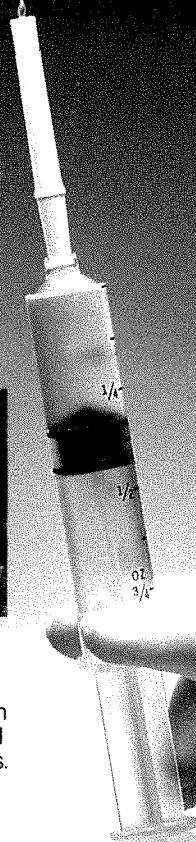
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PRECAUTIONS: General: Consult the Absorbable Gelatin Sponge, USP product labeling for complete information for use prior to utilizing the thrombin-saturated-sponge procedure.

Pregnancy-teratogenic effects: Pregnancy Category C. Animal reproduction studies have not been conducted with Thrombin, Topical USP (Bovine origin). It is also not known whether Thrombin, Topical USP (Bovine origin) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Thrombin, Topical USP (Bovine origin) should be given to a pregnant woman only if clearly indicated.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Allergic reactions may be encountered in persons known to be sensitive to bovine materials.

DOSAGE AND ADMINISTRATION: General: Solutions of THROMBOGEN Thrombin may be prepared in sterile distilled water or isotonic saline. The intended use determines the strength of the solution to prepare. For general use in plastic surgery, dental extractions, skin grafting, neurosurgery, etc., solutions containing approximately 100 units per ml are frequently used. For this, 10 ml of diluent added to the 1,000 unit package is suitable. When bleeding is profuse, as from cut surfaces of liver and spleen, concentrations as high as 1,000 to 2,000 units per ml may be required. Intermediate strengths to suit the needs of the case may be prepared by selecting the proper strength package and dissolving the contents in an appropriate volume of diluent. In many situations, it may be advantageous to use THROMBOGEN Thrombin in dry form on oozing surfaces.

CAUTION: Solutions should be used immediately upon reconstitution. However, the solution may be refrigerated at 2-8°C for up to three hours. The following techniques are suggested for the topical application of THROMBOGEN Thrombin.

1. The recipient surface should be sponged (not wiped) free of blood before THROMBOGEN Thrombin is applied.
2. A spray may be used or the surface may be flooded using a sterile syringe and small gauge needle. The most effective hemostasis results when the THROMBOGEN Thrombin mixes freely with the blood as soon as it reaches the surface.
3. In instances where THROMBOGEN Thrombin in dry form is needed, the vial is opened by removing the metal ring by flipping up the plastic cap and tearing counterclockwise. The rubber-diaphragm cap may be easily removed and the dried THROMBOGEN Thrombin is then broken up into a powder by means of a sterile glass rod or other suitable sterile instrument.
4. Sponging of treated surfaces should be avoided in order that the clot remain securely in place. THROMBOGEN Thrombin may be used in conjunction with Absorbable Gelatin Sponge, USP as follows:
 1. Prepare THROMBOGEN Thrombin solution of the desired strength.
 2. Immerse sponge strips of the desired size in the THROMBOGEN Thrombin solution. Knead the sponge strips vigorously with moistened gloved fingers to remove trapped air, thereby facilitating saturation of the sponge.
 3. Apply saturated sponge to bleeding area. Hold in place for 10 to 15 seconds with a pledget of cotton or a small gauze sponge.

THROMBOGEN Spray Kit: The THROMBOGEN Spray Kit contains one sterile vial of THROMBOGEN Thrombin, one sterile vial of isotonic saline diluent, one sterile disposable syringe and one sterile syringe spray tip. The kit may be used as follows:

1. Remove the Tyvek® blister lid from the outermost tray by pulling up at the indicated corner. The sterile inner tray can then be lifted out or introduced into the sterile field.
2. Remove the Tyvek® blister lid from the inner tray to expose the sterile contents.
3. Using the sterile syringe equipped with the needle, draw the desired amount of saline diluent from the vial into the syringe.
4. Inject the saline diluent into the THROMBOGEN Thrombin vial from the syringe to reconstitute the THROMBOGEN Thrombin powder.
5. When the THROMBOGEN Thrombin is completely dissolved, draw the THROMBOGEN Thrombin solution into the syringe.
6. Remove and discard the needle, affix spray tip by pushing down and turning clockwise until the spray tip locks in place.
7. Depress the syringe plunger in a normal fashion to dispense the THROMBOGEN Thrombin solution through the tip in a fine spray.
8. Alternatively, to facilitate using the THROMBOGEN Thrombin with an Absorbable Gelatin Sponge, USP the THROMBOGEN Thrombin solution may be dispensed directly from the syringe into a sterile container vs. attaching the spray tip. When THROMBOGEN Thrombin is needed in the dry form, the vial is opened and the dried THROMBOGEN Thrombin pellet should be broken up into a powder with a sterile glass rod or other suitable instrument.

Caution: Federal law prohibits dispensing without a prescription.

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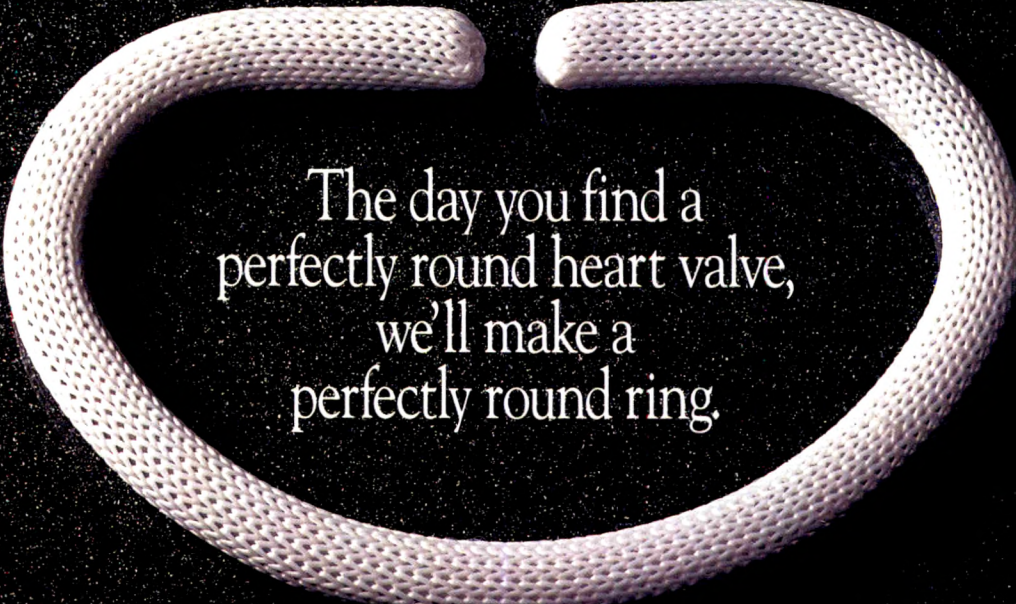
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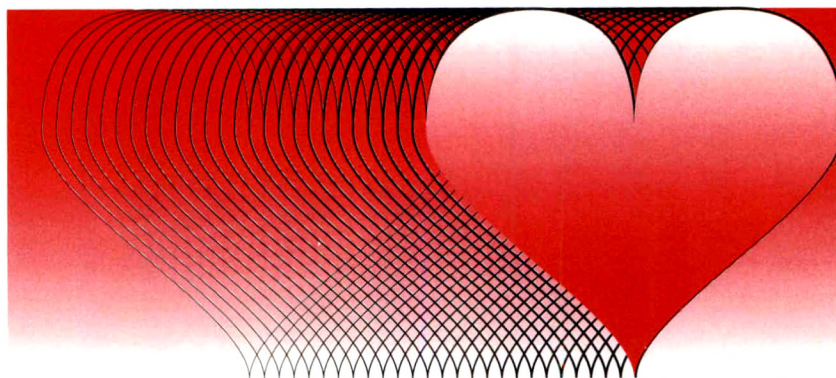
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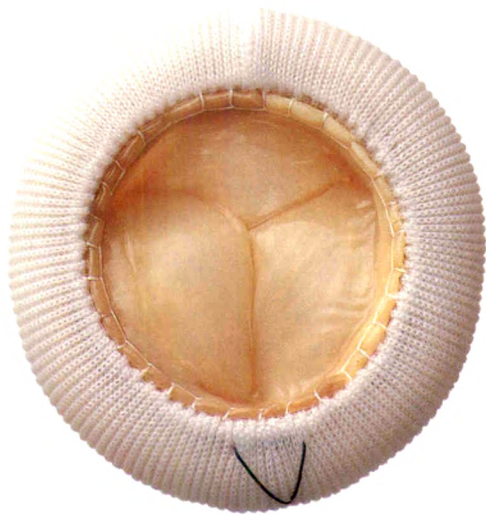
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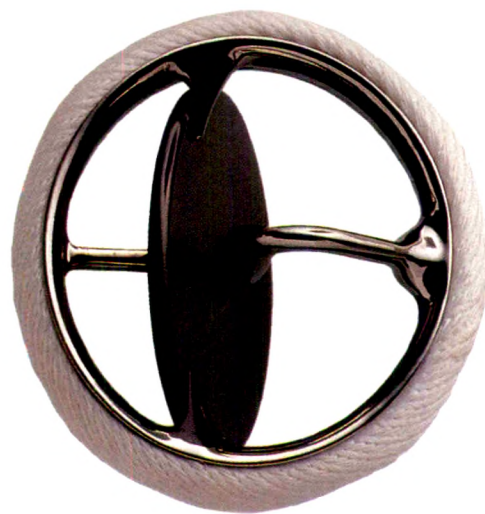
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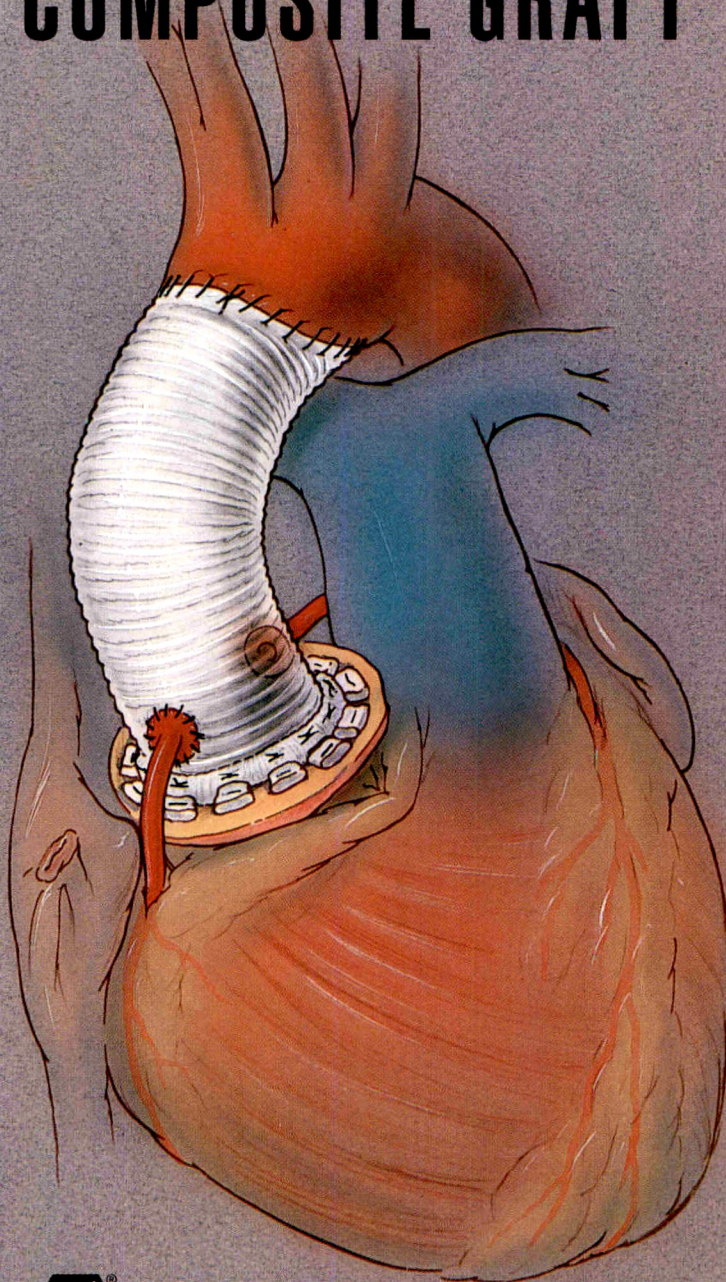
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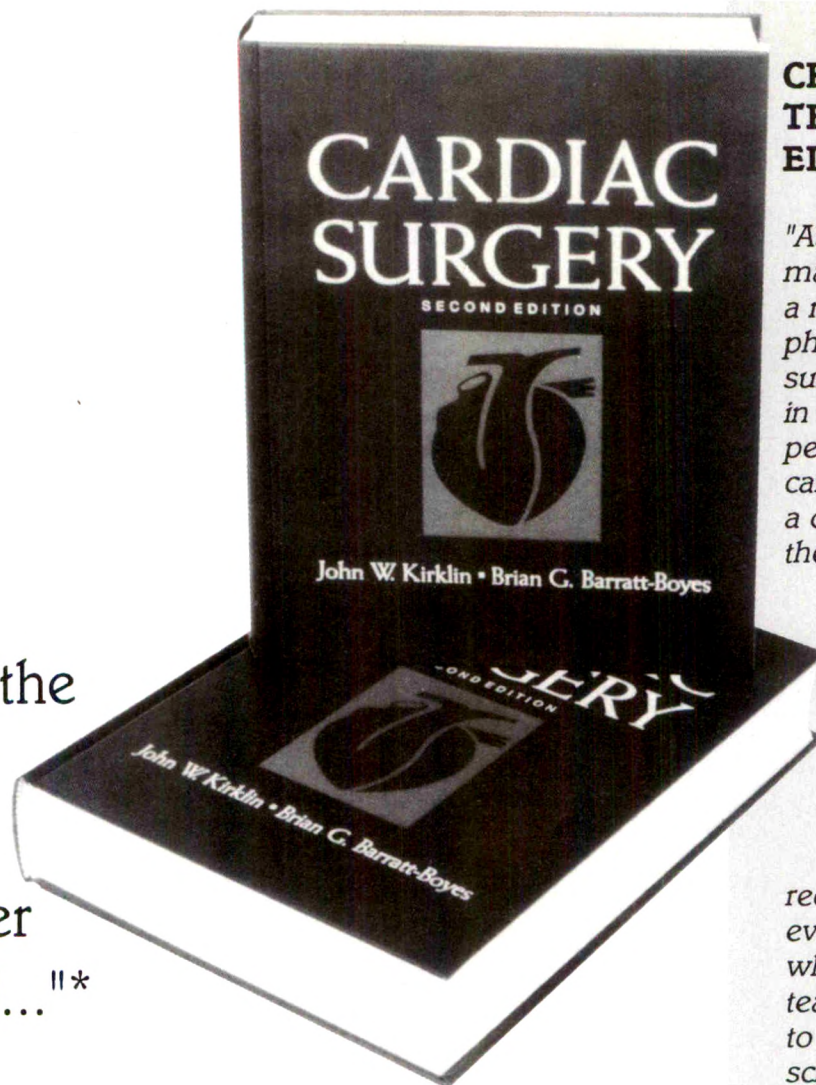


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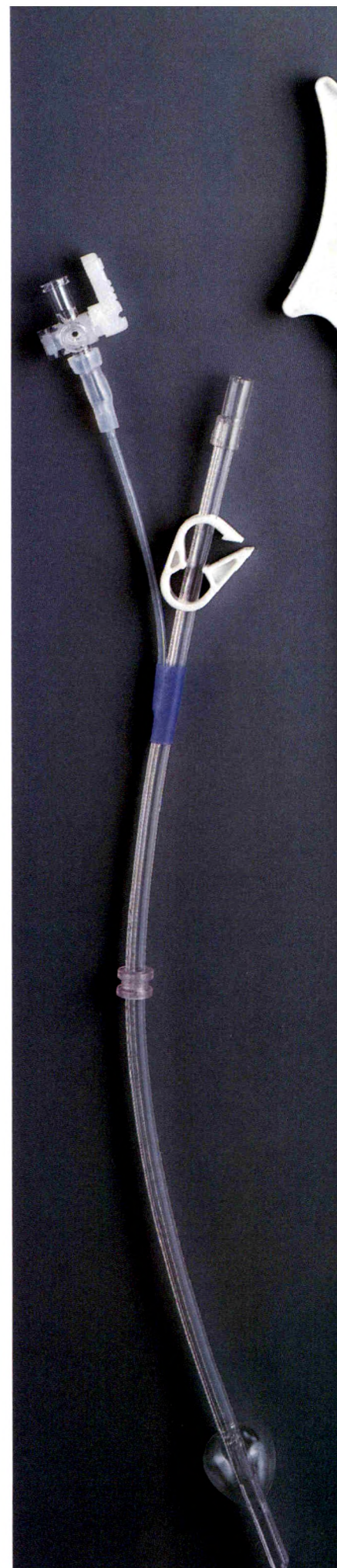
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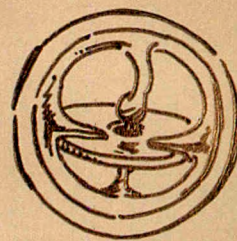
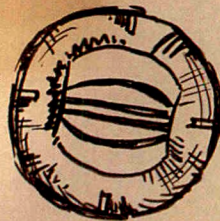
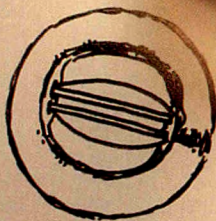
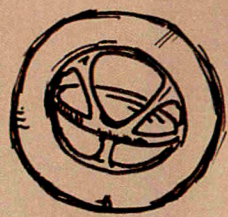
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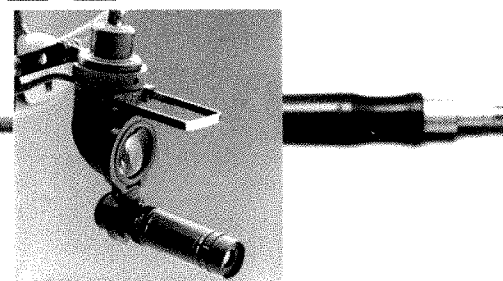
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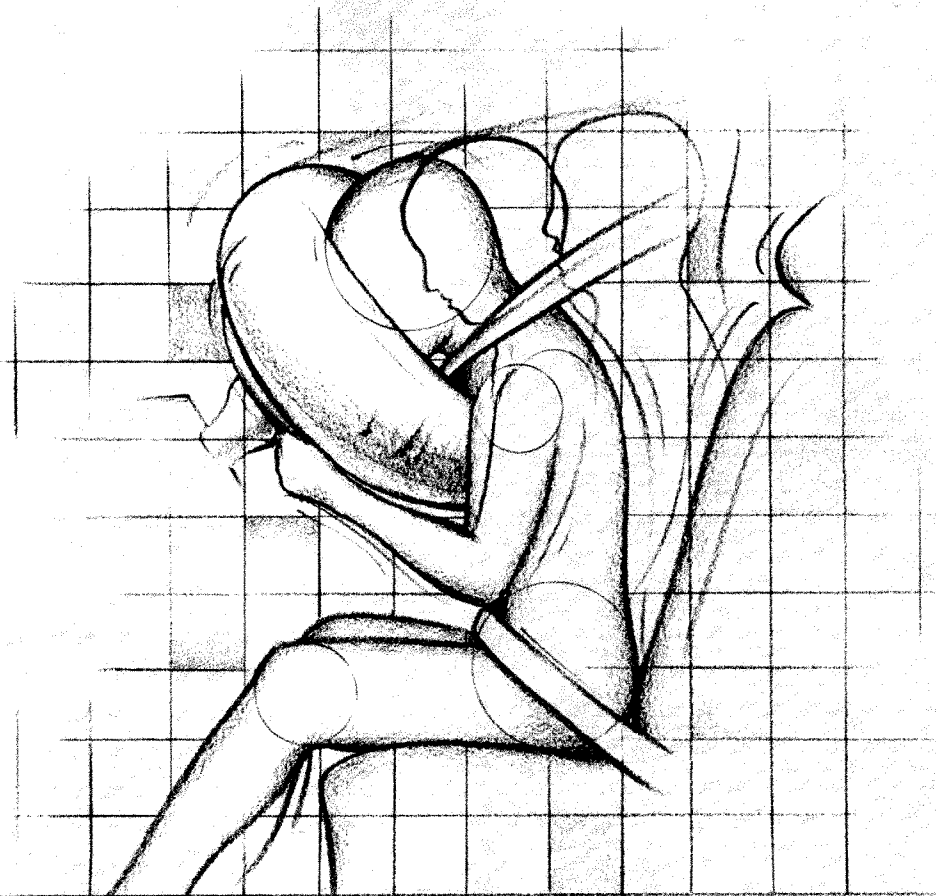
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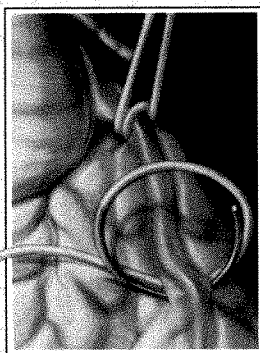


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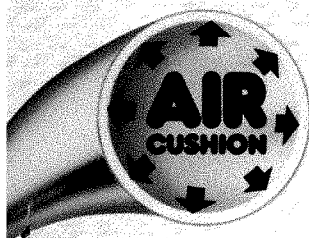
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- ☐ A manuscript for an *original article* ordinarily should not exceed 26 double-spaced typewritten pages, and should be proportionally shorter the more illustrations and tables that are included.
- ☐ The *text* for case reports should be *no more* than 4 double-spaced typewritten pages. If tables or illustrations are included, the text must be reduced. The text for a "how to do it" article should be even briefer, but with detailed illustrative material. Case reports and "how to do it" articles that exceed the allowable length will not be considered for publication.
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For information on this meeting, entitled "Pathophysiology & Techniques of Cardiopulmonary Bypass," contact CREF, PO Box 23220, San Diego, CA 92193; or telephone (619) 541-1444.

■ Forty-second Annual Meeting of the American College of Cardiology, Anaheim, California—March 14-18, 1993

For information on this meeting, contact American College of Cardiology, 9111 Old Georgetown Rd, Bethesda, MD 20814; or telephone (800) 253-4636.

■ Neurohumoral Effects of Profound Hypothermia in Infant Heart Surgery, London, England—March 18-19, 1993

For information on this meeting, contact The Postgraduate Centre, National Heart and Lung Institute, Dovehouse St, London SW3 6LY, England; or telephone 071-351 8172 (facsimile: 071-376 3442).

■ Le Club Mitrale, Paris, France—March 27-April 3, 1993

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ica International, 620 Newport Center Dr, Suite 575, Newport Beach, CA 92660; or telephone (714) 640-5870, extension 28 (facsimile: (714) 759-6911).

■ One Hundred Thirteenth Annual Meeting of the American Surgical Association, Baltimore, Maryland—April 1-3, 1993

For information on this meeting, contact American Surgical Association, Department of Surgery, CB 7245, University of North Carolina, 136 Burnett-Womack Building, Chapel Hill, NC 27599; or telephone (919) 966-4320 (facsimile: (919) 966-6009).

■ American College of Surgeons, Montreal, Canada—April 25-28, 1993

For information on this meeting, contact American College of Surgeons, 55 E Erie St, Chicago, IL 60611; or telephone (312) 664-4050 (facsimile: (312) 440-7014).

■ Seventy-third Annual Meeting of the American Association for Thoracic Surgery, Chicago, Illinois—April 26-28, 1993

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■ World Congress on Diseases of the Chest, Amsterdam, the Netherlands—June 13-18, 1993

For information on this meeting, contact XVII World Congress on Diseases of the Chest, International Academy of Chest Physicians & Surgeons, 3300 Dundee Rd, Northbrook, IL 60062-2348.

■ Nineteenth Annual Meeting of The Western Thoracic Surgical Association, Carlsbad, California—June 24-26, 1993

For information on this meeting, contact The Western Thoracic Surgi-

cal Association, 13 Elm St, Manchester, MA 01944; or telephone (508) 526-8330 (facsimile: (508) 526-4018).

■ **Le Club Mitrale, Paris, France, June 26–June 3, 1993**

For information on this live teleconference, contact Margo Irr, ProMedica International, 620 Newport Center Dr, Suite 575, Newport Beach, CA 92660; or telephone (714) 640-5870, ext 28 (facsimile: (714) 759-6911).

■ **Twenty-first World Congress of The International Society for Cardiovascular Surgery, Lisbon, Portugal—September 12–15, 1993**

For information on this meeting, contact ISCVS XXIst World Congress, Congress Secretariat, 13 Elm St, Manchester, MA 01944.

■ **Seventh Annual Meeting of The European Association for Cardio-Thoracic Surgery, Barcelona, Spain, September 20–22, 1993**

For information on this meeting, contact EACTS Executive Secretariat,

Le Fugon, PO Box 51, rue Cardinal Richaud, F-33028 Bordeaux, France; or telephone 33 56 50 67 36 (facsimile: 33 56 50 67 43).

■ **Neurological Injury and Pediatric Cardiac Surgery (including results of the prospective Boston Circulatory Arrest Study), Boston, Massachusetts, September 30–October 2, 1993**

For information on this meeting, contact Laura Young, Department of Cardiac Surgery, Children's Hospital, 300 Longwood Ave, Boston, MA 02115; or telephone (617) 735-7930 (facsimile: (617) 735-6742).

■ **Fifty-ninth Annual Scientific Assembly, American College of Chest Physicians, Orlando, Florida—October 24–28, 1993**

For information on this meeting, contact American College of Chest Physicians, 3300 Dundee Rd, Northbrook, IL 60062; or telephone (708) 498-1400 (facsimile: (708) 498-5460).

■ **Fortieth Annual Meeting of the Southern Thoracic Surgical Association, Panama City Beach, Florida—November 4–6, 1993**

For information on this meeting, contact Southern Thoracic Surgical Association, 401 N Michigan Ave, Chicago, IL 60611-4267; or telephone (312) 644-6610 (facsimile: (312) 321-6869).

■ **Sixty-sixth Scientific Session of the American Heart Association, Atlanta, Georgia, November 8–11, 1993**

For information on this meeting, contact American Heart Association, 7320 Greenville Ave, Dallas, TX 75231; or telephone (214) 373-6300 (facsimile: (214) 373-3406).

■ **Thirtieth Annual Meeting of The Society of Thoracic Surgeons, New Orleans, Louisiana, January 31–February 2, 1994**

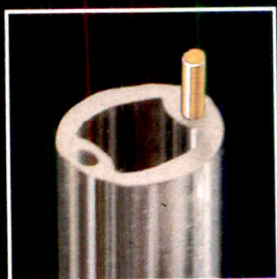
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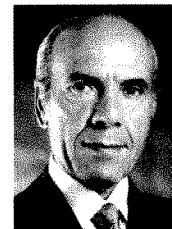
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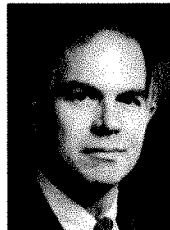
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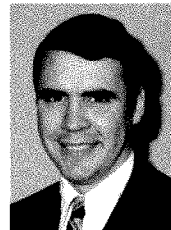
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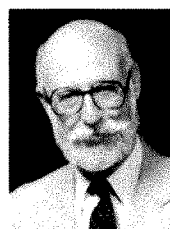
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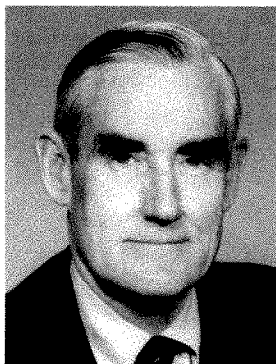
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RBRVS and Cardiothoracic Surgery



National physician payment reform, coronary artery bypass demonstration projects that bundle reimbursements, and multimillion dollar budgets for developing new practice guidelines; these are but a few of the current federal initiatives being developed to control the ever-escalating cost of health care. It is true that with a 10% annual growth rate, health care spending could go from 666 billion dollars in 1990 to one trillion dollars in 1995 and 1.5 trillion dollars or 16.4% of the gross national product by the year 2000. By comparison, the total US national budget was only 1.35 trillion in 1990. Add this to the fact that roughly 37 million Americans, most of them employees of small businesses or their dependents, have no health coverage at all and 20 million more are without adequate coverage for health care needs. It is not surprising, therefore, that there were more than 20 bills in Congress this year dealing with health care reform and considerable activity in many states on new health payment plans. Space does not permit detailed discussion of any of these specific programs; I would like, however, to comment briefly on recent cost control initiatives initiated by the Health Care Financing Administration (HCFA).

In 1989 Congress passed the Omnibus Budget Reconciliation Act (OBRA '89). As a result of this Act, the Medicare Fee Schedule under which physicians' work is now being valued was developed. This fee schedule is a result of a study by the Harvard School of Public Health and modified by HCFA after receiving comments from many interested parties, including our specialty. The Health Care Financing Administration released the final rule on November 15, 1991; it became effective on January 1, 1992, and this is the evaluation method currently used to value all physicians' Medicare payments.

One of the primary goals of the Medicare payment policy, in addition to reducing overall federal spending, was to increase payments to primary care physicians, especially general and family practitioners, and reduce

payments to practitioners of procedurally oriented disciplines such as thoracic surgery, ophthalmology, and anesthesia. Based on the Resource-Based Relative Value Scale (RBRVS), HCFA has projected a 27% to 28% increase in Medicare payments to primary care physicians and a 27% to 28% reduction in payments to ophthalmologists, radiologists, and thoracic surgeons during the interval of 1991 to 1996. At our own institution, we have seen a 14% decrease in the average Medicare payments for coronary bypass operations between 1991 and 1992. We anticipate further reduction in payment for these procedures of 16% between 1992 and 1996. Fortunately, because of our geographic situation, we had only a 2% reduction in the same coronary artery bypass Medicare payments from 1987 to 1991. Surgeons in other areas of the country, however, have experienced Medicare payment reductions of up to 29% for the period of 1987 to 1991 due to a number of initiatives including Medicare's "over-valued procedure concept." Thus, cardiothoracic surgeons in some areas of the country may experience Medicare fee reductions for coronary artery bypass of 50% to 55% between 1987 and 1996. Although the foregoing figures are a worst case scenario, HCFA has estimated that 70% of cardiothoracic surgeons will sustain overall reductions in excess of 25%, and 9% will experience a devaluation of more than 50%.

Our Society has been extremely fortunate in having as chairman of its Government Relations Committee Dr George E. Miller, Jr, who has devoted literally thousands of hours of his time over the last six years to this very complicated maze of initiatives in the area of physician payment reform. Dr Miller has testified on many occasions before HCFA and the Physicians Payment Review Commission (PPRC).

Doctor Miller and his very able Vice-Chair, Dr Jack Matloff, along with the other members of our Government Relations Committee, felt that the initial Harvard study under the direction of Dr William Hsiao did not correctly derive the work values (time X's intensity) of many of our cardiothoracic surgical procedures. The Committee felt that there were several reasons for these incorrect work values in the initial Harvard study. First, in the development of the work component of each service, 100 "thoracic and cardiovascular surgeons" were asked to value time and intensity for 22 cardiothoracic and vascular procedures. The names of these 100 surgeons were obtained from the AMA listing of self-declared specialists in thoracic and cardiovascular surgery; therefore, some of the individuals who were surveyed for relative work values either were not boarded in our specialty or were not actively performing the operations they were asked to review. Second, the relative work values for each of the 22 procedures were determined by survey of the "skin-to-skin" time and skin-to-skin intensity of the operation. The intensity value was an estimation for the procedure in

Photograph of Dr Gott © Leonard L. Greif, Jr.

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question as it related to the placement of a single-chamber pacemaker with transvenous electrodes. This pacemaker procedure was the single "benchmark" for all cardiac, general thoracic, and vascular procedures. Compared with the benchmark, the work values for the great bulk of our cardiothoracic procedures appeared to our committee to be significantly reduced. A third concern of our committee was the fact that although skin-to-skin times and intensities were surveyed by the Harvard group, the period from the patient's entrance into the operating room until the skin incision was made was estimated at 20 minutes and given a value of half the intensity of performing a history and physical. This seemed to be a significant under-estimate of intensity and time for that particular period. Also, the time and intensity during the period from the closure of the skin to entry into the intensive care unit (approximately 20 to 30 minutes) were not included at all. And, finally, the work intensity during the postoperative stabilization period of a cardiothoracic procedure (first half-hour in the intensive care unit) was, in our opinion, markedly underestimated. All of the foregoing factors lead to a compression of the overall intensity scale, ie, simple procedures ranked too high and many of our very involved procedures ranked too low.

There was a second review of these work intensities by a small group of cardiothoracic surgeons, and again, our Government Relations Committee was concerned about the amount of data that were obtained by estimation rather than actually determining precise time and work intensity factors for most of the operations we perform.

The Government Relations Committee and the elected leadership felt that the Harvard study submitted to HCFA needed further modification, and our Society, in turn, commissioned in 1989 a new, very detailed time-intensity evaluation of approximately 45 cardiothoracic procedures by Abt Associates, Inc, of Cambridge, MA. Abt surveyed more than 200 cardiothoracic surgeons from our Society on these 45 surgical procedures. Careful attention was paid to the work intensity of not only skin-to-skin activity, but also the high-risk, high-intensity work periods immediately before and after the intrathoracic activity. The Abt study concluded that the Harvard study had undervalued general thoracic procedures by 4%, vascular procedures by 18%, and cardiac procedures by 25%. This study was submitted by our Society to HCFA; initially, it was praised by both HCFA and PPRC, but subsequently when HCFA released the final fee schedule on November 15, 1991, we found that few of the Abt study determinations were adapted to the HCFA payment schedule. The actual modifications in HCFA's final rule of November 1991 resulted in general thoracic procedures being upgraded by roughly 2%, vascular procedures by 4.5%, and cardiac procedures by 3%. Because of HCFA's concern regarding the validity of the 1992 fee schedule, HCFA termed the final rule "an interim rule" and invited further comments to be submitted by March 25, 1992. Following receipt of these comments, "Refinement Panels" were convened in May 1992, during which representatives of each specialty met with panels consisting of members of HCFA, their regional payment intermediary medical di-

rectors, and representatives of other medical specialties. During these panel meetings, each procedural code addressed in the specialties' refinement comments was reviewed. As of this writing, it is our understanding that the latest iteration of the final rule, which will become effective January 1, 1993, will be published later this Fall and will reflect the results of all input to date.

With an annual "ratcheting down" of Medicare payments for most of our current surgical procedures over the next four years, one of the few areas for budgetary expansion might relate to the volume of procedures performed. Thus HCFA has established the concept of Volume Performance Standards that allow for very modest growth of procedural volume countrywide each year.

Cardiothoracic surgeons in certain areas of the country who have clinical practices without a high percentage of Medicare patients will probably not experience a significant budgetary turndown. On the other hand, cardiac groups doing principally coronary artery bypass surgery in certain areas of the country may sustain a fairly severe reduction in practice income during the period from 1987 to 1996. This will be particularly difficult for academic cardiothoracic programs in those same geographic areas. With the very marked reduction in NIH research funding, most of us involved with university-based cardiothoracic residency training programs support, to a considerable degree, our research laboratories from patient income. Clearly, the funding of cardiothoracic research in most university centers will be reduced during the remainder of this decade. Also during the congressional session just completed there were new bills, considered but not passed, that would preferentially "weight" direct Medicare graduate medical education payments to hospitals to financially favor training slots for primary care physicians as opposed to procedurally oriented physicians. These new congressional initiatives will certainly reappear in new health care reform bills in 1993; the clear intent by Congress is to increase the funding for pediatric, internal medicine, and family practice training programs and reduce funding for surgical training programs. These potential budgetary reductions for thoracic surgical training come at a time when the Joint Conference on Graduate Training in Thoracic Surgery has just recommended increasing the training period in our specialty from two to three years. Facilitating this change in thoracic training over the next few years may be more difficult because of a reduction in direct Medicare funding to hospitals.

Our Society has been very fortunate in having highly dedicated members of the Government Relations Committee. In addition to the Chairman and Vice-Chairman, I need to single out two other members, Dr Sidney Levitsky and Dr Thomas Bartley, who have devoted a great amount of time to the activities of the Committee. These individuals have presented accurately and carefully the concerns of thoracic surgeons over the last several years to the critical health care agencies in Washington. Doctor Miller and his committee feel, though, that at the present time with all of the potentially restrictive health care mandates on the horizon, it is essential for our Society to select a full-time, Washington-based representative dedi-

cated and committed to our specialty's interest. In a recent mail survey of our Society's members, 94% of the 393 respondees supported a more active political stance by The Society. At the last meeting of The Society of Thoracic Surgeons Council in mid-October, there was a unanimous decision to proceed with the concept of full-time representation for our specialty in Washington.

Obviously, our specialty will see some major changes during the rest of this decade; changes in the organization of our clinical practices, changes in cardiothoracic training programs, and changes in the type and the amount of cardiothoracic research. It is apparent that it will be

important for our Society to become very proactive in the medical initiatives of the new Clinton administration.

A handwritten signature in black ink, reading "Vincent L. Gott". The signature is written in a cursive, flowing style with a large initial "V".

Vincent L. Gott, MD
President, The Society of Thoracic Surgeons

Incidence and Recurrence of Gastrointestinal Cytomegalovirus Infection in Heart Transplantation

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Cytomegalovirus (CMV) infection of the upper gastrointestinal tract is a major cause of morbidity in heart transplant recipients. Since April 1985, 201 patients underwent heart transplantation at our institution. Immunosuppressive therapy was with a triple drug regimen of cyclosporin A, prednisone, and azathioprine. Fifty-three of these patients had upper gastrointestinal symptoms, which primarily consisted of abdominal pain or nausea and vomiting despite prophylactic treatment with antacids, H_2 blockers, or both. A total of 79 esophagogastroduodenoscopies were performed in this group; 15 patients required more than one esophagogastroduodenoscopy for recurrent symptoms. Of these 53 patients with persistent gastrointestinal symptoms, 16 (30.2%) had diffuse erythema or ulceration of the gastric mucosa (14), esophagus (1), and duodenum (1) with biopsy results that were positive for CMV on viral cultures

(incidence, 8%). All patients with positive biopsy results were treated with intravenous ganciclovir at a dose of $10 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ in two divided doses for a period of 2 weeks. Recurrence developed in 6 patients (37.5%) and necessitated repeated therapy with ganciclovir. None of the 16 patients died as a result of gastrointestinal CMV infection. Patients who were seronegative for CMV and received a seropositive heart experienced earlier clinical manifestation of CMV infection. Infection of the upper gastrointestinal tract with CMV is a major cause of morbidity in cardiac transplant patients that may progress to a life-threatening complication if left untreated. Early diagnosis with esophagogastroduodenoscopy and biopsy for viral cultures is essential for documentation and proper management.

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Cytomegalovirus (CMV), a member of the herpesvirus group, is a ubiquitous virus that can be transmitted through a variety of ways including virus-infected grafts [1]. It is believed that 50% to 80% of adults carry the virus; however, it is almost always latent and asymptomatic unless the carrier becomes immunologically compromised. Transplant recipients in whom an active CMV infection develops from a contaminated organ appear to require a course of immunosuppression to manifest the infection [2].

Series of CMV infection in the transplant population demonstrate an incidence between 15% and 100% [3, 4]. Manifestations of CMV infection include pneumonitis, retinitis, gastrointestinal ulceration and hemorrhage, hepatitis, bone marrow suppression, central nervous system disease, and fever. Cytomegalovirus also predisposes the transplant recipients to infection by other organisms. Mortality in the heart and heart-lung transplant patients with symptomatic CMV infection has been reported to be between 29% and 40%. With the addition of cyclosporin A to the immunosuppressive regimens, it appears that the morbidity of symptomatic CMV infections and the mortality of all infections have been reduced [5, 6].

Gastrointestinal manifestations of CMV infection in the immunosuppressed transplant population have been described involving the esophagus, stomach, duodenum, and colon. The histologic and pathologic appearance of CMV infection involving the gastric mucosa has been documented [7]. In this series, the clinical presentation, diagnostic management, therapy, and outcome of CMV infection of the upper gastrointestinal tract in heart transplant recipients are described.

Material and Methods

From April 1985 to May 1991, 201 patients underwent 205 heart transplantations, including one in the heterotopic position (Table 1). Mean age at transplantation was 46.4 years (range, 2 days to 66 years). There were 175 male and 26 female patients. Serologic test for CMV using immunofluorescence assay was performed in serum samples of donors and recipients at the time of transplantation. The 30-day operative mortality was 3.5%. Average follow-up period was 38.0 months (range, 4 to 77 months).

The immunosuppression regimen consisted of cyclosporin A, azathioprine, corticosteroids, and rabbit antithymocyte globulin. Preoperative cyclosporin A was administered orally at a dose of 4 mg/kg , and administration was continued postoperatively at $5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ to keep serum levels between 300 and 350 ng/mL. Azathioprine was given orally at a preoperative dose of 4 mg/kg and continued postoperatively at 2 to 3 mg

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Table 1. Indication for Heart Transplantation (205 transplants in 201 patients)

Preoperative Diagnosis	No. of Patients (%)
Ischemic	92 (45.8)
Idiopathic	67 (33.3)
Viral	17 (8.5)
Congenital	9 (4.5)
AGAS	4 (2.0)
Postpartum	1 (0.5)
Other	11 (5.5)

AGAS = accelerated graft atherosclerosis.

$\text{kg}^{-1} \cdot \text{day}^{-1}$. Methylprednisolone, 500 mg, was administered intraoperatively and continued at 125 mg intravenously every 12 hours for the first 24 hours. After this period, prednisone administration was started at a dose of $1.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ and tapered to $0.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$. Rabbit antithymocyte globulin was administered intramuscularly at a dose of 200 mg every day for the first 3 days, except in the neonate recipient who did not receive rabbit antithymocyte globulin.

Intravenous human immune globulin was given at a dose of $1 \text{ g} \cdot 10 \text{ kg}^{-1} \cdot \text{day}^{-1}$ for 7 days. Patients also received prophylaxis against the probable association of corticosteroids and ulceration of the upper gastrointestinal tract with antacids, H_2 blockers, or both.

During this period of time, 53 patients underwent a total of 79 esophagogastroduodenoscopies (EGDs). These patients' primary symptoms were midepigastic or right upper abdominal pain with or without persistent nausea and vomiting. One patient had an acute abdomen and another had upper gastrointestinal bleeding. Biopsies of the gastrointestinal mucosa were performed whenever diffuse mucosal erythema, ulceration, or nodules were observed. The presence of CMV was confirmed by growing the virus in culture media, or by immunofluorescent studies using murine anti-CMV antigen monoclonal antibodies in mucosal tissue preparations.

Intravenous therapy with ganciclovir was initiated when the CMV infection was documented. The initial dose was $10 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ over 14 days. After this initial treatment, if the patient continued to be symptomatic, ganciclovir therapy was extended for another 14 days.

Results

Of the 201 patients, 16 had development of CMV infection of the gastrointestinal tract (incidence, 8%). The presenting symptoms in these 16 patients were variable. The most common presenting symptom (6 patients) was diffuse upper abdominal pain sometimes radiating to the right upper quadrant. In addition, 3 patients had similar abdominal pain associated with nausea and vomiting, and 2 had only nausea and vomiting. Two patients had diffuse upper abdominal pain associated with fever. One patient had abdominal pain and hiccups. One patient was admit-

ted with a bleeding gastric ulcer, and 1 patient had an acute abdomen. Exploratory laparotomy in the latter patient revealed a perforated pyloric ulcer and an inflamed gastric mucosa.

Cytomegalovirus serology for donors and recipients was obtained at the time of transplantation (Table 2). There were 3 patients who were seropositive and received seropositive hearts. Seven recipients were seronegative and received seropositive hearts. Five patients were seropositive and received seronegative hearts, and only 1 patient was seronegative and received a seronegative heart.

Fifteen patients had the diagnosis of CMV infection of the upper gastrointestinal tract made from mucosal biopsies at the time of EGD. Only the patient with the perforated pyloric ulcer had the diagnosis made from the biopsy at the time of the exploratory laparotomy. Midepigastic pain developed in this patient 9 months later. Esophagogastroduodenoscopy with biopsy revealed recurrent CMV gastritis. Fourteen patients had documented gastritis at the time of the EGD. In addition to the gastritis, 2 patients had esophagitis and duodenitis, 1 patient had duodenitis, 1 patient had severe ulcerative esophagitis, and 1 patient had a bleeding gastric ulcer (see Table 2).

The mean interval between transplantation and the first episode of CMV infection for the entire group was 10.6 months (range, 1.2 to 56.9 months). The average interval for the 7 patients who were seronegative and received a seropositive heart was only 2.0 months. The average interval for the other 9 patients was 17.3 months ($p < 0.01$; Mann-Whitney U test). The average cumulative dose of ganciclovir for all patients for the first documented CMV infection was 13.4 g (range, 6.3 to 22 g). Three patients required modification of the initial dose: in 2 patients because of development of neutropenia and in 1 patient because of deteriorating renal function. Six patients (37.5%) experienced at least one recurrence. Average period for first recurrence was 2.6 months (range, 0.13 to 8.4 months). All the recurrent infections were diagnosed as gastritis except in 1 patient who also had duodenitis. Two patients experienced a second recurrence, and 1 of these experienced third and fourth recurrent infections. This last patient was treated with additional ganciclovir for a period of 28 days. The subgroup of patients with recurrence was small, and risk factors for recurrence have not been identified.

None of the 16 patients with CMV infection died as a result of the CMV infection. The actuarial survival (Cutler-Ederer method using the Gehan test) for the patients who had gastrointestinal CMV infection and those patients who did not have gastrointestinal CMV infection was not significantly different (Fig 1).

Comment

Cytomegalovirus infections can affect all transplant recipients and any other patient who is immunosuppressed. Cytomegalovirus infection either may be reactivated if the recipient was already seropositive or may develop as a

Table 2. Patients With Upper Gastrointestinal Cytomegalovirus Infections

Patient	CMV Status		Time to First Infection (mo)	Findings	Ganciclovir (cumulative dose in grams)	Recurrence (findings)
	Donor	Recipient				
1	+	+	28.5	Perforated pyloric ulcer	14.0	Gastritis
2	+	+	56.9	Gastritis	14.2	...
3	-	+	31.2	Esophagitis, gastritis, duodenitis	6.3	...
4	+	-	1.3	Gastritis	22.4	...
5	+	-	1.4	Gastritis	9.75	...
6	+	-	2.8	Gastritis	11.2	Gastritis
7	-	+	3.0	Gastritis, duodenitis	25.2	Gastritis
8	+	-	1.2	Gastritis	17.7	Gastritis
9	-	+	1.6	Gastritis, bleeding ulcer	16.0	...
10	+	+	9.0	Gastritis, esophagitis	11.2	...
11	+	-	1.6	Gastritis	9.6	...
12	-	-	16.5	Esophagitis	22.0	...
13	-	+	7.4	Gastritis	6.3	...
14	+	-	3.5	Esophagitis, gastritis, duodenitis	8.4	...
15	-	+	2.2	Duodenitis	6.3	Gastritis, duodenitis
16	+	-	2.0	Gastritis	14.7	Gastritis

CMV = cytomegalovirus.

primary infection if the recipient was seronegative. Since the advent of cyclosporin A the frequency of symptomatic infections has decreased, although it appears that heart recipients had CMV infections more often than patients who received liver and renal transplants [8]. The morbidity and mortality associated with CMV infection usually are secondary to superinfections by bacterial and fungal agents [9].

Cytomegalovirus in our heart transplant population was recovered on 89 occasions from various bodily fluids (blood, urine, nasopharyngeal, tracheobronchial aspirations; and gastrointestinal biopsy specimens). The upper gastrointestinal tract was the most common source.

Multiple agents including intravenous immunoglobu-

lin, interferon, acyclovir, and a CMV vaccine have been evaluated to treat CMV infection. Winston and associates have suggested that the immune globulin may have some prophylactic efficacy against CMV; however, its efficacy in the treatment of CMV infections has not been established [10, 11].

Ganciclovir (9-[2-hydroxy-1-(hydroxymethyl)ethoxymethyl] guanine) appears to be the agent of choice in the treatment of established CMV infections, especially for the treatment of CMV infections affecting the gastrointestinal tract [12]. Ganciclovir is an acyclic nucleoside that has been shown to be effective against laboratory and clinical strains of CMV [13]. It inhibits DNA polymerase and in this way prevents replication of the virus. However, it does not eliminate the virus from the host. Therefore, recurrences of CMV infections are always possible. Adverse reactions described with the use of ganciclovir are uncommon but include neutropenia, thrombocytopenia, impaired renal function, grand mal seizure, and hypotension [14]. Renal function should be taken into consideration when calculating the appropriate dosage, and frequent white blood count monitoring is also advisable.

Endoscopy of the upper gastrointestinal tract is essential in cardiac transplant patients with upper abdominal complaints. Examination and viral cultures of the gastrointestinal mucosa are of extreme importance to confirm the correct diagnosis.

Cytomegalovirus infections may be associated with accelerated graft atherosclerosis. In a review of heart transplant recipients, accelerated graft atherosclerosis was found to be significantly more severe in the CMV infec-

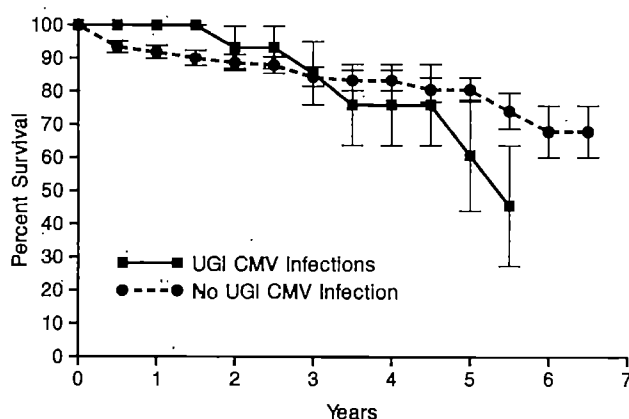


Fig 1. Actuarial survival of 185 patients without cytomegalovirus (CMV) infection and 16 patients with gastrointestinal (UGI) CMV infection.

tion group [15]. Six of our patients with CMV infections of the upper gastrointestinal tract have been found to have accelerated graft atherosclerosis. However, this series is not large enough to reach a conclusion regarding a relation between CMV infections and accelerated graft atherosclerosis or rejection.

In summary, 201 patients underwent heart transplantation at our institution. Fifty-three patients had abdominal findings requiring EGD and 1 patient needed an exploratory laparotomy. For the patients who required EGD, the diagnosis of CMV infection of the upper gastrointestinal tract was made with mucosal biopsies. One patient required biopsy of a perforated pyloric ulcer for diagnosis of CMV infection. Patients who were seronegative for CMV and received a heart of a seropositive donor had earlier manifestations of upper gastrointestinal tract CMV infections. All patients were treated with ganciclovir for a minimum of 2 weeks. Recurrences occurred in 37.5% and were treated with repeated doses of ganciclovir. No maintenance ganciclovir was required between episodes. There was minimal morbidity in this group associated with the use of ganciclovir and no mortality associated with CMV infections. Infection of the stomach was the most common manifestation of CMV in this group of patients, and the stomach was the most common site of recurrence. Early diagnosis should be made with EGD and mucosal biopsies. Ganciclovir is the treatment of choice at this time.

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DISCUSSION

DR WALTER H. MERRILL (Nashville, TN): In some centers the 2-week treatment is routinely followed by another 2 weeks at a lower dose of ganciclovir, and I noticed that you did not do that in your center. Could you comment on the treatment protocol?

DR ARABIA: We followed up these patients in two different ways. First, we followed them up symptomatically during that first period of 2 weeks and then by repeat endoscopy. If at the time of endoscopy, we found no evidence of inflammation, the

cultures were negative, and the patient was symptomatically better, we did not continue therapy.

DR MERRILL: Did you come up with a diagnosis or cause of abdominal distress in those patients who did not have cytomegalovirus infection?

DR ARABIA: Yes, there were a large number of patients who ended up having peptic ulcer disease and nonspecific gastritis.

Leukocyte Depletion in a Neonatal Model of Cardiac Surgery

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Neonatal cardiac surgical procedures continue to be associated with a considerable incidence of severe post-operative ventricular dysfunction. The role of neutrophils in mediating such injury has recently been proposed but remains controversial. The present study was undertaken to examine the potential benefits of leukocyte depletion for myocardial preservation using an *in situ*, *in vivo* porcine model of neonatal cardiac surgery. Sixteen 3- to 5-day-old piglets, 8 controls and 8 leukocyte-depleted animals (LD group), underwent 90 minutes of hypothermic ischemia. Mechanical leukocyte filtration during cardiopulmonary bypass reduced the granulocyte count in the initial perfusate to 0.7% of controls. This

was associated with a reduction in leukocyte sequestration in the coronary vascular bed ($p < 0.005$), a decrease in myocardial creatine kinase release ($p < 0.02$), and a reduction in coronary vascular resistance ($p < 0.03$). These changes in physiological response to ischemia were associated with improved postischemic recovery of left ventricular systolic function in LD animals ($p < 0.05$), although there was no significant improvement in diastolic function. Application of this technique in neonatal cardiac operations may improve myocardial protection and reduce the associated morbidity and mortality.

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Although neutrophils are involved primarily in the maintenance of the immune system, under certain conditions of altered physiology they may cause damage to host tissue. The accumulation of polymorphonuclear leukocytes in myocardium after ischemia has been recognized for many years [1]. However, their pathogenic role in myocardial ischemia/reperfusion injury remains unclear.

Neutrophils have been implicated in the etiology of irreversible myocyte injury after coronary reperfusion in studies demonstrating a decrease in myocardial infarct size associated with a reduction in neutrophil population or neutrophil function [2, 3]. In contrast, their role in reversible postischemic ventricular dysfunction is still controversial [4, 5], with alteration of neutrophil function and population leading to differing results. However, the interaction of cardiopulmonary bypass (CPB) and myocardial ischemia in cardiac operations may change the response of neutrophils to ischemic myocardium and increase the susceptibility of the heart to injury.

This study examines the effect of mechanical leukocyte depletion during ischemia and reperfusion on postischemic myocardial function in an *in situ*, *in vivo* porcine model of neonatal cardiac surgery.

Material and Methods

Three- to 5-day-old farm-raised Yorkshire-Hampshire cross piglets were separated from the sow on the day of the experiment. All animals received humane care in compliance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research and the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH Publication No. 85-23, revised 1985).

Piglets were premedicated with ketamine hydrochloride (44 mg/kg), and anesthesia was induced by inhalation of 2% isoflurane. A tracheostomy was performed, the trachea was intubated, and mechanical volume ventilation was initiated with an inspired oxygen fraction of 1.0. Maintenance anesthesia was provided by isoflurane inhalation (0.5% to 1.0%). The femoral artery and vein were cannulated to record systemic arterial and venous pressures.

A median sternotomy was performed, and the ductus arteriosus was ligated. Both vagal nerves were then divided to reduce the autonomic reflex influence of left ventricular (LV) function. Heparin sodium (3 mg/kg) was given before proximal ligation of the hemiazygos vein and insertion of an 8F catheter downstream into the coronary sinus. The distal coronary sinus was then ligated at its junction with the right atrium. Coronary sinus flow was returned to the piglet through an 8F catheter positioned in the distal superior vena cava. Coronary flow was measured by an ultrasonic transit-time flow probe (Transonic 2R; Transonic Systems Inc, Ithaca, NY) placed in line with the coronary sinus catheter.

Pulse transit ultrasonic dimension transducers (Physio-

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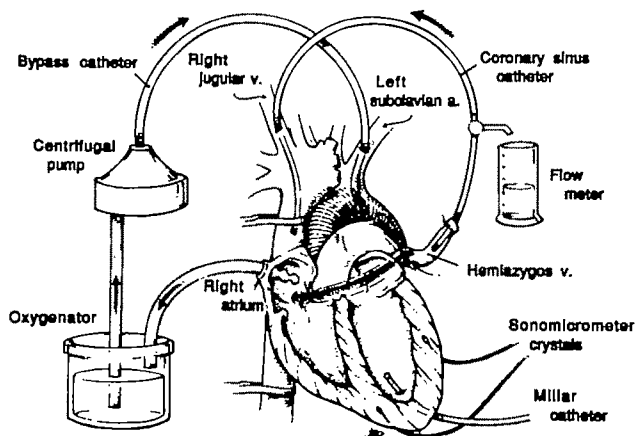


Fig 1. The experimental instrumentation.

logical Monitoring Systems; Duke Medical Center, Durham, NC) connected to a sonomicrometer (model 120; Triton Technology Inc, San Diego, CA) were positioned subendocardially to record the LV short-axis dimension. Instantaneous LV pressures were recorded by a Millar micromanometer catheter (model PC-350; Millar Instruments, Houston, TX) passed into the ventricle through its apex. Tapes were placed around both the inferior and superior venae cavae to allow manipulation of ventricular preload during evaluation of ventricular function.

Pressure manometry catheters were positioned in the left atrium through its appendage and in the pulmonary artery through the right ventricular infundibulum. Measurement of cardiac output was achieved by a flow probe (Transonic 8R) placed around the main pulmonary artery.

Systemic temperatures were controlled using a heating/cooling blanket and by adjustment of the perfusate temperature while the animal was on CPB.

Cardiopulmonary Bypass

The CPB circuit was constructed using tubing with an internal diameter of 1/4-inch (6.25-mm) connected to a centrifugal pump head (Bio-Medicus BP-80; Bio-Medicus, Eden Prairie, MN), a temperature-controlled bubble oxygenator (Bentley-5 pediatric blood oxygenator; Bentley American, Irvine, CA), and a pediatric extracorporeal blood filter (Pall LPE-1440; Pall Biomedical Inc, Fajardo, PR) (Fig 1). Leukocyte depletion was achieved in the treatment group by three leukocyte filters (Pall RC100) positioned in parallel on the arterial limb of the bypass circuit.

The circuit was primed with 800 mL of heparinized (3 mg/100 mL) whole blood, and the circulating hematocrit was maintained between 0.25 and 0.28 with lactated Ringer's solution. Vascular access for CPB was attained by inserting a 10F cannula into the descending aorta through the left subclavian artery and by positioning a single right atrial cannula (20F) through the right atrial appendage. Cardiopulmonary bypass was commenced at flow rates of 80 to 100 mL · kg⁻¹ · min⁻¹ with maintenance of a perfusion pressure of 40 to 45 mm Hg and a mixed venous saturation of 70% to 80%. Systemic arterial blood gases were corrected on CPB using alpha-stat control.

Piglets were cooled to 22°C rectal temperature before cross-clamping of the aorta, after which cold crystalloid cardioplegia (20 mL/kg of Johns Hopkins cardioplegic solution) was instilled in an antegrade fashion through the aortic root. Total circulatory arrest was then commenced for closure of the patent foramen ovale. A patent foramen ovale was present in every animal and was repaired by direct suture through a longitudinal right atriotomy. Extracorporeal circulation was resumed after a 30-minute period of total circulatory arrest, after which slow systemic rewarming was commenced before removal of the aortic cross-clamp after 90 minutes of myocardial ischemia. Myocardial temperatures were maintained less than 15°C by the topical application of 4°C saline solution.

Myocardial reperfusion was initiated with warm blood (36°C) at 30 mm Hg perfusion pressure; the pressure was increased gradually over 1 minute to 45 mm Hg. Myocardial reperfusion was continued for 30 minutes in the beating nonworking state before weaning from CPB. Atrial pacing (150 beats/min) was used for all hearts with an intrinsic rate of less than 150 beats/min.

Measurements and Calculations

CORONARY LEUKOCYTE SEQUESTRATION AND MYOCARDIAL CREATINE KINASE RELEASE. Coronary leukocyte sequestration and myocardial creatine kinase release were calculated by measuring the difference between the systemic arterial and coronary venous concentrations of leukocyte count and creatine kinase activity, respectively. Leukocyte counts were measured by Coulter counter analysis (Coulter STKR; Hialeah, FL). Leukocyte sequestration was measured in number of cells per minute per gram of LV wet weight. Creatine kinase activity, measured at 37°C, was measured in international units per minute per gram of LV wet weight.

CORONARY VASCULAR RESISTANCE INDEX. Coronary blood flow was measured at a mean coronary perfusion pressure of 40 to 45 mm Hg. Previous experiments in this newborn model revealed a linear relationship between coronary flow and coronary perfusion pressure in this pressure range. Previous experiments in this model also showed that 90% or more of the coronary sinus blood originated from the left ventricle; therefore, coronary vascular resistance (CVR) was standardized as:

$$\text{CVR (dynes} \cdot \text{s} \cdot \text{cm}^{-5} \cdot \text{g LV weight)}$$

$$= (\text{mean aortic pressure} - \text{mean right atrial pressure})$$

$$\cdot 80/(\text{coronary flow/LV wet weight}),$$

where pressure is measured in millimeters of mercury, coronary flow is measured in liters per minute, and LV weight, in grams.

LEFT VENTRICULAR FUNCTIONAL ASSESSMENT. The indices chosen for analysis of LV function were preload recruitable stroke work (representing overall ventricular performance), end-systolic pressure-volume relationship (representing ventricular systolic function), and ventricu-

lar stiffness (representing an inverse relationship to ventricular compliance). These methods of ventricular functional assessment have been shown to be relatively independent of afterload within the physiological ranges encountered in this in vivo model.

MYOCARDIAL WATER CONTENT. Myocardial water content was calculated after incubation of a section of left ventricle at 100°C for 24 hours. It is represented as percent of LV wet weight.

MYELOPEROXIDASE ACTIVITY. Myeloperoxidase activity was calculated on biopsy specimens taken at completion of the experiment by standard spectrophotometric functional assay. Results are presented in micromoles per 10 mg of wet weight of tissue.

Experimental Protocol

Both the control group ($n = 8$) and the group with leukocyte depletion (LD group; $n = 8$) underwent 90 minutes of hypothermic global myocardial ischemia in an in vivo, in situ model of newborn cardiac surgery. Leukocyte kinetics and indices of myocardial injury were studied during coronary reperfusion. Hemodynamic function and ventricular function were assessed for 60 minutes after discontinuation of CPB.

Six separate piglet experiments were performed (3 controls and 3 LD animals) to provide tissue for ultrastructural analysis of the myocardium. Electron microscopy was performed by a single observer blinded to the treatment groups. Specimens were fixed by coronary perfusion with 4°C 3% glutaraldehyde solution in 0.1 mol/L sodium cacodylate buffer (pH 7.4). The samples were stored in 0.1 mol/L sodium cacodylate solution in 7.5% sucrose (pH 7.4) until processed.

Six piglets (3 controls and 3 LD animals) underwent exchange transfusion to study the effects of large-volume transfusion in this newborn model and to examine the consequences of transfusing leukocyte-depleted blood on vascular resistance and myocardial function in the absence of myocardial ischemia. Animals were exchange-transfused twice their calculated blood volume over 1 hour using fresh heparinized adult porcine blood.

Table 1. Comparison of Age and Weight

Variable	Control	LD
Age (d)	4.9 ± 0.40	4.9 ± 0.35
Body weight (kg)	1.81 ± 0.05	1.85 ± 0.05
Heart weight (g)	18.94 ± 0.98	19.93 ± 0.40

LD = leukocyte depletion.

Statistical Analysis

Results are expressed as the mean $\pm$ the standard error of the mean. Differences between groups were tested for significance by Student's *t* test for unpaired samples or repeated-measures analysis of variance, as appropriate.

Results

Sixteen piglets (8 controls and 8 LD animals) underwent the experimental protocol and were weaned from CPB. The mean age of the groups was similar, as were body weight and heart weight (Table 1). During CPB, a relative leukopenia and granulocytopenia developed in the controls. However, the LD animals showed a marked reduction in circulating leukocytes and granulocytes in the initial coronary reperfusion compared with controls (14.3% and 0.7%, respectively), and a significant reduction in circulating granulocytes was maintained during the entire period of coronary reperfusion ($p \leq 0.0005$). Reappearance of granulocytes in the circulation was apparent in both groups after complete systemic rewarming and discontinuation of CPB, with similar rates of increase in granulocyte numbers in the circulation of both groups (Table 2).

Leukocyte sequestration across the coronary vascular bed was demonstrated in control animals throughout the period of coronary reperfusion with peak accumulation recorded 5 minutes after removal of the cross-clamp ($237 \pm 86 \times 10^3$ leukocytes $\cdot \text{min}^{-1} \cdot \text{g}^{-1}$ of left ventricle) (Fig 2). In contrast, LD animals showed a significant reduction in coronary leukocyte sequestration ($p \leq 0.005$), manifested by demargination during initial reperfusion ($-73 \pm 21 \times 10^3$ leukocytes $\cdot \text{min}^{-1} \cdot \text{g}^{-1}$ of left ventricle) fol-

Table 2. Systemic Arterial White Blood Cell Counts

Measurement ^a	Leukocytes (No. cells $\times 10^3/\text{mL}$)		Granulocytes (No. cells $\times 10^3/\text{mL}$)	
	Control	LD	Control	LD
Prime	$13,146 \pm 1300$	677 ± 150	$6,047 \pm 854$	14 ± 4
Before bypass	$8,633 \pm 797$	$7,324 \pm 469$	$4,426 \pm 603$	$3,619 \pm 470$
Myocardial reperfusion (min)				
5	$4,231 \pm 429$	603 ± 111	552 ± 140	4 ± 2
35	$3,522 \pm 268$	948 ± 140	457 ± 72	31 ± 8
90	$3,270 \pm 366$	965 ± 177	499 ± 90	87 ± 26

^a The first two measurement entries are as follows: prime = white blood cell count in cardiopulmonary bypass circuit immediately before the start of extracorporeal circulation; before bypass = white blood cell count immediately before cardiopulmonary bypass.

LD = leukocyte depletion.

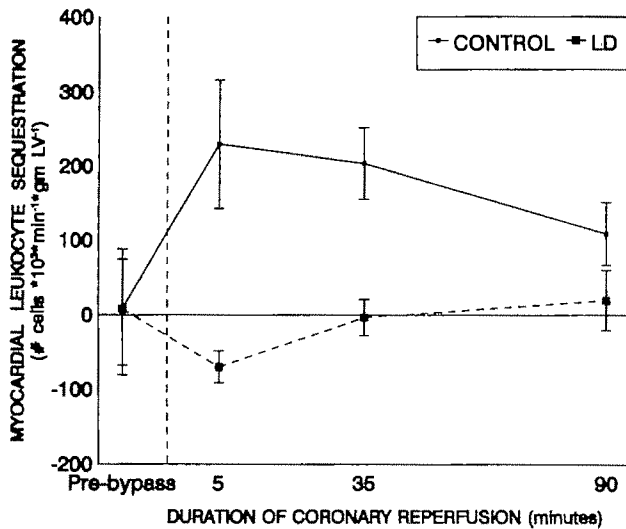


Fig 2. Myocardial leukocyte sequestration across the coronary vascular bed before the onset of cardiopulmonary bypass and during coronary reperfusion. (LD = leukocyte depletion.)

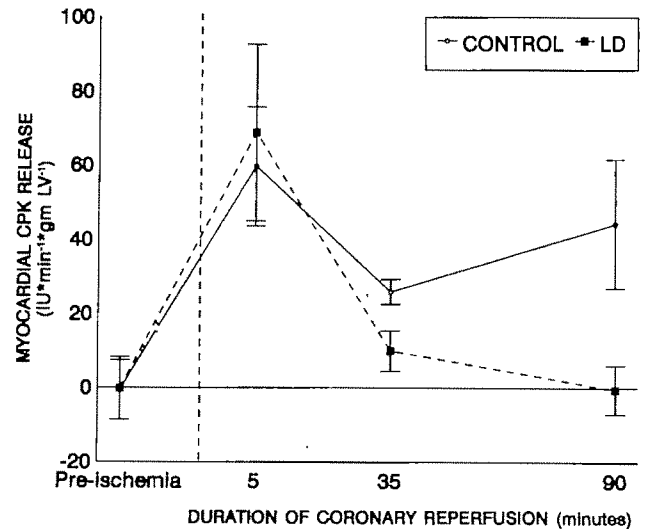


Fig 3. Release of myocardial creatine kinase (CPK) into the coronary venous blood. Release was calculated as the gradient between the systemic arterial and the coronary sinus blood. (LD = leukocyte depletion.)

lowed by minimal sequestration throughout the remainder of the period of observation.

Myocardial myeloperoxidase activity demonstrated significantly greater activity in control piglets ($69 \pm 4 \mu\text{mol}/10 \text{ mg}$ of left ventricle) compared with LD animals ($27 \pm 4 \mu\text{mol}/10 \text{ mg}$ of left ventricle; $p \leq 0.005$) and confirmed the greater accumulation of granulocytes in controls. Previous experiments in which biopsy specimens were taken from hearts before and after flushing with normal saline solution after ischemia and reperfusion revealed no significant difference in myeloperoxidase activity after flushing. This suggests that circulating leukocytes participate little in myocardial myeloperoxidase activity after ischemia.

The pattern of myocardial creatine kinase release during coronary reperfusion was also different between groups. Enzyme release was similar during initial reperfusion ($59.7 \pm 16.0 \text{ IU} \cdot \text{min}^{-1} \cdot \text{g}^{-1}$ of left ventricle in controls and $77.4 \pm 23.8 \text{ IU} \cdot \text{min}^{-1} \cdot \text{g}^{-1}$ of left ventricle in the LD group). However, there was a significant increase in myocyte creatine kinase leakage in controls at 35 and 90 minutes of reperfusion (25.9 ± 3.4 and $44.3 \pm 17.3 \text{ IU} \cdot \text{min}^{-1} \cdot \text{g}^{-1}$ of left ventricle, respectively) compared with LD animals (7.2 ± 5.5 and $3.7 \pm 6.62 \text{ IU} \cdot \text{min}^{-1} \cdot \text{g}^{-1}$ of left ventricle, respectively) ($p \leq 0.02$) (Fig 3).

Coronary vascular resistance index was reduced in both groups during initial coronary reperfusion compared with baseline, but subsequently rose to greater than preischemic values by 35 minutes of reperfusion in controls and remained elevated throughout the remainder of the experiment (Fig 4). In contrast, the LD group showed a gradual increase in coronary vascular resistance index during the experiment, but it never was greater than baseline and remained significantly lower than that in controls ($p \leq 0.03$). Hemoglobin concentrations were similar in both groups (Table 3).

These changes in coronary reperfusion were associated with an alteration in ventricular function. Postischemic recovery of LV performance (preload recruitable stroke work) was improved in the LD animals at 15 and 60 minutes after CPB compared with controls ($70\% \pm 5\%$ and $65\% \pm 4\%$, respectively, in controls, and $96\% \pm 5\%$ and $94\% \pm 6\%$ in LD animals; $p \leq 0.01$) (Fig 5). This was associated with significant improvement in the end-systolic pressure-volume relationship, controls recovering $57\% \pm 6\%$ and $66\% \pm 4\%$ at 5 and 60 minutes, respectively, compared with LD piglets with recovery of $84\% \pm 6\%$ and $89\% \pm 5\%$ at the same time points ($p \leq 0.01$) (Fig 6). However, no significant difference in myo-

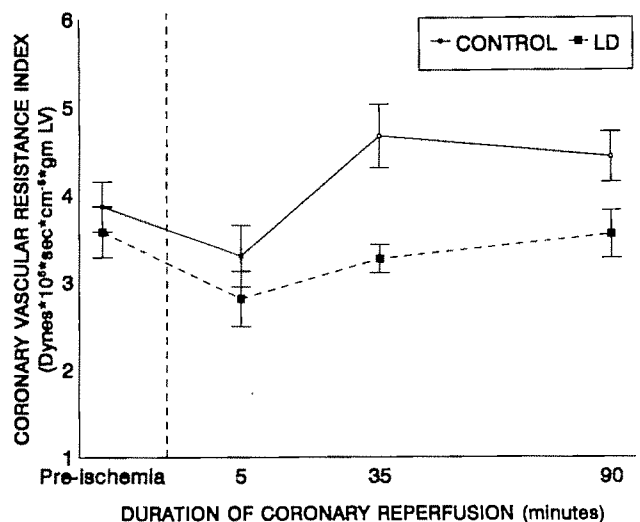


Fig 4. Coronary vascular resistance measured before cardiopulmonary bypass (Pre-ischemia) and during coronary reperfusion. These measurements were standardized to the weight of the left ventricle as described in the text. (LD = leukocyte depletion.)

Table 3. Systemic Arterial Hemoglobin Concentration

Group	Before Bypass	Hemoglobin Concentration (g/dL)		
		Start	Reperfusion	90 Minutes
Control	9.6 ± 0.48	10.1 ± 0.42	10.6 ± 0.39	10.7 ± 0.67
LD	9.3 ± 0.60	10.3 ± 0.40	11.0 ± 0.38	10.9 ± 0.21

LD = leukocyte depletion.

cardial oxygen consumption was identified ($p \leq 0.3$) despite similar heart rates in both groups (Table 4).

In contrast to these improvements in ventricular function, ventricular stiffness was not significantly different between groups, and LV water content showed similar increases in both controls ($79.7\% \pm 0.4\%$) and LD animals ($78.96\% \pm 0.5\%$) ($p \leq 0.3$) compared with baseline ($77.9\% \pm 0.2\%$).

Hemodynamic monitoring demonstrated a significant reduction in pulmonary vascular resistance in the LD animals compared with controls over the course of the observation period ($p \leq 0.05$), although there was no significant difference in systemic vascular resistance between groups ($p \leq 0.5$) (Table 5). However, mean pulmonary artery pressure was not significantly different between groups before or after ischemia.

Electron microscopy revealed predominantly reversible myocardial injury in all piglets. There was no increase in irreversible damage in either group.

Exchange transfusion of homologous blood to newborn piglets not undergoing CPB and myocardial ischemia resulted in no significant change from baseline in LV function or CVR. Leukocyte depletion of exchange-transfusion blood also resulted in no significant change in these variables after exchange transfusion.

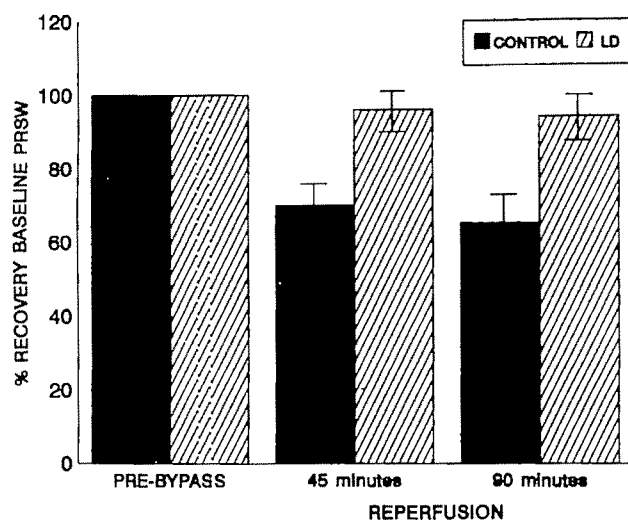


Fig 5. Preload recruitable stroke work (PRSW) expressed as percent recovery of baseline. Measurements were performed 15 minutes and 60 minutes after discontinuation of cardiopulmonary bypass. (LD = leukocyte depletion.)

Comment

The role of neutrophils in ischemia/reperfusion injury of the myocardium remains uncertain, but their ability to cause tissue injury in response to inflammatory mediators is established [7]. Neutrophils are capable of reversible and irreversible cellular injury by release of oxygen-derived free radicals and lysosomal enzymes in response to neutrophil activation. However, whether these mechanisms are important in the etiology of postischemic ventricular dysfunction after a cardiac operation is not known.

Neutrophil-endothelial cell adhesion is critical to neutrophil-mediated tissue injury because it allows sufficiently high concentrations of these cytotoxic agents to accumulate between the neutrophil and endothelial cell. Myocardial ischemia and CPB both promote neutrophil-endothelial cell adhesion, thereby predisposing the myocardium to such an injury.

The release of inflammatory mediators in response to CPB has been known for many years [8]. However, the effect of these mediators on neutrophil adhesion was not known. We have recently documented increased expression of the neutrophil cell surface adhesion receptor subunit CD18 in a newborn model of CPB, suggesting an increased number of neutrophil CD11b/CD18 surface receptors available for neutrophil-endothelial cell interaction (unpublished data). This finding demonstrates that the systemic inflammatory response initiated by the con-

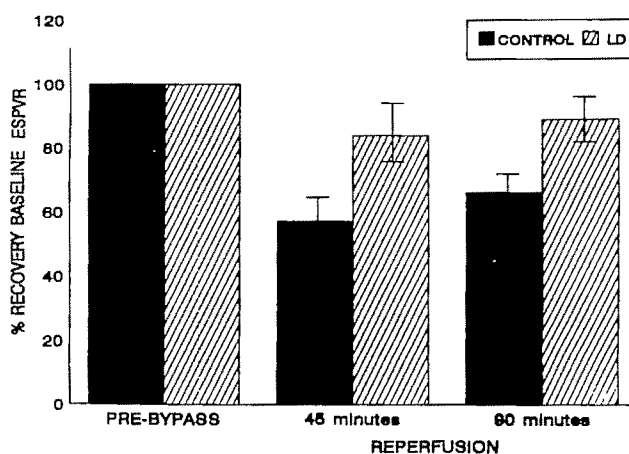


Fig 6. End-systolic pressure-volume relationship (ESPVR) expressed as percent recovery of baseline. The time points for assessment were as in Figure 5. (LD = leukocyte depletion.)

Table 4. Myocardial Oxygen Consumption and Heart Rate

Variable	Control			LD		
	Before Bypass	Reperfusion		Before Bypass	Reperfusion	
		35 Minutes	90 Minutes		35 Minutes	90 Minutes
MVO ₂ (mL/g LV wet weight)	0.0319 ± 0.0020	0.0289 ± 0.0018	0.0288 ± 0.0030	0.0325 ± 0.0023	0.0302 ± 0.0021	0.0300 ± 0.0030
Heart rate (beats/min)	153 ± 3	156 ± 2	153 ± 3	154 ± 2	155 ± 3	151 ± 2

LD = leukocyte depletion; LV = left ventricular; MVO₂ = myocardial oxygen consumption.

tact of blood with the extracorporeal circuit may predispose the myocardium to neutrophil-mediated tissue injury. Intramyocardial complement activation induced by myocardial ischemia [9] may cause the heart to become a target for these activated neutrophils by opsonizing myocardial endothelium with C3bi and by promoting neutrophil chemotaxis. In response to complement activation or as a direct effect of ischemia, increased expression of endothelial intracellular adhesion molecule and endothelial-leukocyte adhesion molecule after ischemia may further promote endothelial-neutrophil interaction. However, the rate of surface expression of endothelial cell receptors during ischemia is reduced by hypothermia, and the importance of this expression in cardiac surgery is unknown.

The present study demonstrates that leukocyte sequestration occurs within the coronary vascular bed after global hypothermic ischemia in an in vivo, in situ model of cardiac surgery. Leukocyte accumulation during coronary reperfusion began early during myocardial reperfusion and peaked at the first recording, 5 minutes after removal of the cross-clamp. This early myocardial leukocyte sequestration during cardiac operations is similar to that described by Semb and colleagues [10] in 1990. However, in the present study, myocardial leukocyte accumulation continued for the duration of the 90-minute period of coronary reperfusion. Similar temporal patterns of leukocyte accumulation during coronary reperfusion have also been reported in models of myocardial infarction [11], in which rapid early accumulation of neutrophils is followed by progressive deposition, with peak myeloperoxidase activity demonstrable at 6 hours after coronary reperfusion.

The cause of the demargination of leukocytes seen in the LD group during initial reperfusion is unknown. However, this study suggests that leukocytes themselves play a part in the accumulation of neutrophils within the coronary vascular bed by a positive feedback mechanism. The reduction in the circulating leukocyte population appears to reduce the tendency for neutrophils to sequester in the coronary vascular bed. This effect is possibly due to a reduction in local chemotactic agents such as leukotriene B₄, platelet-aggregating factor, or superoxide anions, which are known to be generated by neutrophils during coronary reperfusion [10, 12], or by a reduction in endothelial cell surface expression of adherence receptors. Leukocyte demargination is thereby able to occur early during coronary reperfusion in response to the release of local agents such as adenosine from myocytes or in response to elevated levels of myocardial catecholamines during coronary reperfusion. The reason for the persistent reduction in leukocyte sequestration is presumably a result of the continued reduction in the circulating neutrophil population, which results in reduced neutrophil exposure to the myocardium, combined with a continued reduction of neutrophil-endothelial cell interaction. However, there was an increase in leukocyte sequestration throughout coronary reperfusion in the LD group as circulating leukocytes increased in number, and the effect of late exposure of the myocardium to leukocytes that return to the circulation after the first 60 minutes after CPB is unknown.

Previous experiments have shown that intracoronary instillation of C5a results in a neutrophil-dependent increase in CVR [13]. The present study demonstrated a similar, although less pronounced, leukocyte-dependent

Table 5. Pulmonary Vascular Resistance and Systemic Vascular Resistance Indices^a

Time	PVRI (dynes · s · cm ⁻³)		SVRI (dynes · s · cm ⁻³)	
	Control	LD	Control	LD
Before bypass	5.80 ± 0.58	5.76 ± 0.89	19.73 ± 2.16	18.88 ± 1.48
Myocardial reperfusion (min)				
35	16.16 ± 1.63	12.10 ± 1.70	22.08 ± 1.88	20.62 ± 3.47
60	14.69 ± 0.68	10.70 ± 0.87	20.60 ± 1.41	18.21 ± 2.01
90	14.69 ± 0.87	10.68 ± 1.16	20.50 ± 1.99	18.33 ± 2.91

^a Both indices were calculated using surface area tables for neonatal piglets [6].

LD = leukocyte depletion; PVRI = pulmonary vascular resistance index; SVRI = systemic vascular resistance index.

rise in CVR after 90 minutes of hypothermic ischemia. The increased neutrophil-endothelial cell interaction present in both studies may account for these changes in vascular resistance, although the mechanism for such a change is unclear. Previous studies [14] have reported that neutrophil capillary plugging, causing capillary "no-reflow" [15], is a cause of increased CVR after irreversible ischemia. However, there are no such reports after reversible ischemia. Release of local vasoactive substances from neutrophils or the loss of normal endothelial cell function may also account for changes in CVR. Leukotrienes C₄ and D₄ and thromboxane A₂ [16, 17] have been shown to be released during postischemic coronary reperfusion and are capable of local vasospasm. These autacoids can be released by neutrophils or neutrophil-entrapped platelets within the coronary vascular bed and thereby may account for neutrophil-mediated changes in CVR. Alternatively, endothelial cell damage may result in reduced production of local vasodilating agents by the endothelium and increased CVR [18]. Such a neutrophil-dependent reduction in endothelium-derived relaxation factor has previously been demonstrated in the coronary vasculature. Whatever the cause of the increase in CVR, it appears to be mediated predominantly by leukocytes independent of myocardial edema, as myocardial water content was not significantly different between groups. Similar reports of a neutrophil-independent increase in capillary permeability during myocardial ischemia support these observations [19].

The improvement in global LV performance (preload recruitable stroke work) and LV systolic function (end-systolic pressure-volume relationship) seen in this study demonstrates that the accumulation of leukocytes during hypothermic myocardial ischemia and normothermic coronary reperfusion in a model of cardiac surgery is associated with reduction in early postischemic ventricular function. Previous studies [4, 5, 20, 21] examining the effects of mechanical leukocyte depletion on regional postischemic myocardial stunning have provided conflicting results. However, the increased tendency to neutrophil-endothelial interaction in this CPB model may increase the degree of leukocyte accumulation in the coronary vascular bed and thus emphasize the benefits of reducing neutrophil population during ischemia and reperfusion.

The cause of the reduction in postischemic systolic ventricular function induced by leukocyte-dependent myocardial injury is unclear. Previous experiments have documented a neutrophil-dependent reduction in systolic ventricular function in response to C5a administration [13], which is associated with an increase in CVR. This effect appears to be short-lived, with rapid return of CVR and systolic function to normal values after discontinuation of C5a injection. These experiments suggest that the reduction in coronary flow in the control group of this study may be a crucial determinant of systolic ventricular function. However, the local release of cytotoxic compounds from neutrophils may also contribute to myocardial injury. Neutrophil-dependent superoxide anion release has been shown to induce postischemic ventricular

dysfunction in Langendorff preparations, and further experiments are necessary to establish the etiology of the myocardial injury. We recognize the possibility of an alteration of right ventricular-LV interaction, caused by a significantly reduced postischemic right ventricular afterload in the LD group, leading to a spurious difference in preload recruitable stroke work and end-systolic pressure-volume relationship. However, although the pulmonary vascular resistance was reduced significantly by leukocyte depletion, the pulmonary artery pressures were not significantly different between groups, and a large alteration in right ventricular-LV interaction between groups is therefore unlikely.

The degree and duration of leukocyte depletion required to achieve these alterations in ischemia/reperfusion injury and the effect of a temporary reduction in circulating granulocytes on the postoperative immunological response are unknown and need further investigation. Recent studies in our laboratory showed that the circulating granulocyte counts in LD piglets return to 68% of those in control animals by 6 hours postoperatively (unpublished data). Despite this rapid return of granulocytes to the circulation, improved myocardial function was preserved for the first 6 hours after myocardial reperfusion. The early reappearance of granulocytes potentially reduces the risk of postoperative infections. In a model of regional stunned myocardium, other investigators [22] have shown that granulocyte counts of 10% of baseline during early coronary reperfusion were sufficient to induce postischemic ventricular dysfunction. However, further studies are required to better document the degree of leukocyte depletion necessary to reduce postischemic ventricular dysfunction during cardiac operations, although these studies do suggest that preoperative acute plasmapheresis [23], in contrast to perioperative mechanical leukocyte depletion, is unlikely to be beneficial.

These results demonstrate that mechanical depletion of the neutrophil population during hypothermic myocardial ischemia and normothermic coronary reperfusion results in improved preservation of postischemic cardiac physiology and myocardial function. The use of leukocyte depletion in clinical cardiac surgery may thereby improve the results of neonatal cardiac surgery in the future.

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DISCUSSION

DR GEORGE L. HICKS, JR (Rochester, NY): My associates and I also are interested in leukocyte filtration but for a different reason. We have seen the possible immunologic effects of transfusions after operation, and you are studying the white cell effect of the filter. What is the exact filtration-pore size of your filter?

Have you looked at the filters and the nature of the cells being trapped? Are you getting white cells, or are you getting a lot of platelets or other debris? I think this may influence what is occurring in your experiment. We do believe that if white cell administration is held to a minimum in the postoperative period, not only can leukocyte injury be decreased but also perhaps the immunologic effects of transfusion components may be decreased.

DR WILSON: Yes, we have examined the filters. I think the function of the leukocyte filter is related more to the polyester fibers than the pore size itself. We may be reducing the platelet

count as well. In this experiment, thrombocytopenia was present in both groups, and there was no significant difference in circulating platelet concentrations between the two groups. However, I cannot disregard the fact that platelet accumulation within the myocardium secondary to leukocyte deposition may well have played a part, and that has been reported previously.

DR RICHARD D. WEISEL (Toronto, Ont, Canada): Dr Wilson, I enjoyed your presentation. I wonder what happens when you finally reperfuse these hearts with normal blood. Are you just delaying rather than ameliorating the detrimental effects of the leukocytes?

DR WILSON: That may well be the case. We have gone on to a further series to look at myocardial function over a 6-hour period, and have found that, in fact, there was no detriment in function over time. These results will be presented eventually.

Subacute Cardiac Rupture: Repair With a Sutureless Technique

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Thirteen patients with ages between 53 and 74 years had development of free wall left ventricular rupture after a myocardial infarction (mean interval, 3.8 days). All patients showed clinical signs of cardiac tamponade. Diagnosis was established by bedside multiple pressure monitoring and echocardiography, which showed pericardial effusion with compression of the right ventricle. Cardiac catheterization was not performed. A new surgical technique was employed for the repair. After the pericardium was opened and cardiac tamponade was relieved, the myocardial tear was identified. A Teflon patch was applied over the area and glued to the heart surface with

a surgical glue (cyanoacrylate). Cardiopulmonary bypass was not used except in a patient with a posterior tear. The method was consistently effective in controlling bleeding from the myocardial tear. All patients survived the operation and were discharged from the hospital a mean of 15 days after the operation. Follow-up extending up to 5 years (mean, 26 months) shows a 100% survival, 11 asymptomatic patients, and 2 patients with mild exertional angina. The technique is a simple, effective, and safe method for repair of subacute cardiac rupture and obviates the need for suturing on an infarcted ventricle.

(*Ann Thorac Surg* 1993;55:20-4)

Subacute cardiac rupture after myocardial infarction requires prompt surgical treatment to relieve cardiac tamponade and repair the myocardial tear. Several reports of successful surgical repair have appeared in the literature [1-8], but, in general, the condition has a fatal outcome. A positive step toward improving results was made by Nuñez and associates [9], who, in 1983, reported a technique of covering the ventricular perforation with a patch fixed to normal myocardium with a continuous polypropylene suture. They achieved a 57% survival.

In 1988, our group [10] reported a case of postinfarction cardiac rupture after myocardial infarction successfully treated with a sutureless technique. The myocardial perforation was covered by a Teflon patch fixed to the heart surface by a biocompatible glue. Extracorporeal circulation was not employed. Since this initial report, the technique has proved to be effective in treating this condition. The glue, butyl-2-cyanoacrylate monomer (Histoacryl blue; B. Braun, Melsungen AG, Germany), does not require an activating substance because it polymerizes when it comes in contact with tissue moisture.

In this article, we report the combined results of two centers treating rupture of the free wall of the left ventricle with this sutureless technique. Nine patients were treated at Hospital "La Paz" in Madrid, a center with large experience in treating cardiac rupture [9, 11], and 4 were treated at Hospital de la Santa Creu i Sant Pau in Barcelona, where the technique originated [10].

Material and Methods

Patient Population

Between November 1986 and April 1991, 13 patients were treated surgically for subacute free wall left ventricular rupture after a myocardial infarction. Ages ranged from 52 to 74 years, with a mean of 64.6 years. Eight patients were men and 5 women. Only 1 patient had history of previous ischemic heart disease.

Myocardial rupture developed a mean of 3.8 days after myocardial infarction (range, 0.5 to 7 days). All patients showed sudden cardiac decompensation with typical signs of cardiac tamponade, including hypotension, cyanosis, and jugular ingurgitation. Two patients sustained cardiac arrest, but they were resuscitated.

Diagnosis of subacute cardiac rupture was made by bedside pressure determinations taken through a Swan-Ganz catheter in 11 patients, and it was confirmed by echocardiography in all patients. Echocardiographic findings included the presence of pericardial effusion and diastolic compression of the right ventricle. A positive pericardiocentesis was obtained in the 8 patients in whom it was performed. Hemodynamic improvement was consistent after this procedure, although only for a short time. After the diagnosis was confirmed, all patients underwent surgical treatment without further studies at the cardiac catheterization laboratory.

Surgical Technique

The surgical protocol was essentially the same throughout the series. After a median sternotomy was performed, the pericardium was opened. Blood and clots were evacuated, and this resulted in dramatic hemodynamic improvement. The heart surface was inspected to localize

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Fig 1. Blood oozing through a posterior myocardial tear (arrow).

the myocardial tear. This was identified in the inferior or posterior aspects of the left ventricle in 7 patients, in the anterior in 3, and in the lateral wall in the remaining 3 patients. The tear in the epicardium ranged between 6 mm and 2 cm, and in only 2 patients was there active, squirting bleeding. In the remaining, small clots were in the area of rupture and oozing was seen coming from the tear (Fig 1). No cardiopulmonary bypass was employed except in 1 patient with a very posterior tear in whom mobilization of the heart produced severe hemodynamic derangement. After exposure of the tear, a few drops of Histoacryl blue were placed over it at surgeon's discretion. Then, the area was covered by a large patch of Teflon felt (measuring about 8×5 cm) and fixed to the heart surface by a few more drops of Histoacryl. Once in place, the patch covered most of the wall where the perforation had occurred. Extra drops of the glue were applied to the patch over the area of the tear. Due to the porous properties of the felt, this maneuver reinforced the tacking of the material over the heart surface. Once dried (less than 30 seconds), the whole area of the tear had a hard mass consistency (Fig 2). The technique was effective in controlling bleeding in all patients. After hemodynamic stabilization, the chest was closed in a routine fashion, leaving two chest tubes and a temporary pacemaker wire.

Results

There were no operative deaths. Postoperative complications included prolonged ventilatory support resulting in sternal dehiscence in 2 patients, low cardiac output requiring inotropic agents in 2 patients, and seizures in 1 patient. Average length of hospital stay was 15 days, ranging from 5 to 40 days.

Five patients had echocardiograms performed between 3 and 7 months after repair. Dyskinesis of the wall affected by the rupture without evidence of pseudoaneurysm was found in 3. One patient underwent cardiac

catheterization several months after operation for professional reasons (airline pilot). The right coronary artery was occluded (he had an inferior rupture), but the rest of the coronary arteries were free of disease. The left ventricle had good motion. The patient with a prior myocardial infarction, who was operated on more than 5 years ago, recently had an echocardiogram that showed normal ventricular function.

Follow-up extends up to 5 years (mean, 26 months) and shows no late deaths and 11 asymptomatic patients. Two patients have mild exertional angina.

Comment

Cardiac rupture was first described by Harvey in 1647 [12]. Morgagni [13] collected 10 cases in his monumental work published in 1769. More than 200 years later, Bates and associates [12] collected 1,200 cases in the literature and reported 20 of their own.

The incidence of cardiac rupture varies between 4% and 24% of all autopsies performed in patients dying of a myocardial infarction [14-17], although higher numbers have been reported in the literature [18]. Cardiac rupture occurs 4 to 10 times more often than rupture of the interventricular septum or a papillary muscle [12, 15], two well-known mechanical complications of myocardial infarction for which surgical treatment is widely and successfully applied. However, surgical treatment of cardiac rupture is still a challenge to most cardiac surgeons because of the high mortality that occurs even before the diagnosis can be made. Cardiac rupture after myocardial infarction is considered to cause more than 25,000 deaths a year in the United States [12].

The approach to treat this problem must be double: first, an awareness of the disease, which has very precise clinical patterns, may help to diagnose many cases before death occurs; and second, the surgical treatment should



Fig 2. Final aspect of the repair with the patch glued over the area of the tear.

be expeditious, simple, and safe. Our patient population does not differ from those of previously published works. Age of the patients had a mean of 64 years, which is in agreement with most of the reported series [9, 15, 16, 18, 19]. Also, the high prevalence of female patients (5 of 13) has been reported previously [14, 16, 17]. In a series of 47 autopsy cases, London and London [16] found that female patients had a 6.9% chance of cardiac rupture after myocardial infarction as compared with 3.8% for men. Griffith and associates [14] found also that it is more likely to occur in women than in men (54% versus 46%). In one study [20], cardiac rupture was responsible for 30% of the deaths due to myocardial infarction of women with ages between 60 and 69 years.

The time of rupture after myocardial infarction in our series was a mean of 3.8 days, ranging from 0.5 to 7 days, with three ruptures occurring during the first 24 hours. In two different studies, Griffith and associates [14] and Shapira and co-workers [20] found 40% of the patients dying within 24 hours of the infarction, but Bates and colleagues [12] found only 50% of the patients had rupture within 4 days, although 87% had rupture by 14 days.

It seems that there is a substantial percentage of patients in whom rupture occurs not as a sudden, explosive, and fatal episode but as an insidious, progressive entity that reveals itself clinically as cardiac tamponade. This "subacute" rupture [4] may leak blood to the pericardium before massive rupture ensues. In this particular subgroup of patients, surgical treatment is possible and lifesaving. Diagnosis must be suspected in any patient recovering uneventfully of a transmural myocardial infarction in whom chest pain develops with sudden collapse. Several electrocardiographic findings have been described as diagnostic of cardiac rupture: bradyarrhythmias (sinus, nodal), increase of the amplitude of the T wave, reduction of the QRS amplitude, reversal to upright of previously inverted T waves, and right bundle-branch block [18, 19, 21], but none is pathognomonic. Signs of cardiac tamponade (pallor, cyanosis, distended neck veins, quiet heart sounds) are always present. Electromechanical dissociation may appear.

Pericardiocentesis is important in the diagnosis and may be lifesaving [3, 4, 7, 12], but confirmation of the rupture is best done by multiple pressure measurements through a Swan-Ganz catheter and by echocardiography.

Beside hemodynamic findings in subacute ventricular rupture have been studied extensively in one of our centers [9, 11] and are as follows: diastolic equalization of right atrial, pulmonary artery, and pulmonary capillary wedge pressures with right atrial pressure elevation (greater than 10 mm Hg); a deep X descent and blunted Y descent in right atrial pressure curves; a decrease in arterial pressure of more than 10 mm Hg during inspiration; and a decrease in the differential pulmonary artery pressure. Echocardiography is an easy and effective method to confirm cardiac tamponade. The presence of pericardial fluid and diastolic compression of the right ventricle are the two most relevant findings.

Once the diagnosis has been established the patient

should be taken to the operating room without delay. Cardiac catheterization and coronary angiography have been performed before successful surgical treatment in some patients [1, 4, 8], but the risks involved are not outweighed by the benefits. Cardiac rupture occurs in patients with small infarcts [14, 22] and poor collateral circulation [18]. Most of the patients do not have history of previous ischemic heart disease, and the process frequently affects patients with single-vessel disease [9]. Of our patients, only 1 had history of a myocardial infarction before the one that originated the rupture, and the only patient with coronary angiography had normal coronary arteries except for occlusion of the vessel irrigating the area of rupture, as in the patients operated on by Pífarre and associates [8]. The presence of fresh thrombosis in the vessel is a typical finding [16, 18]. However, other authors report severe, generalized disease in cases of cardiac rupture [12, 15]. The left anterior descending coronary artery has been implicated as the responsible vessel in some studies [14, 23], although in our experience, as in that of others [9, 12, 15, 17, 18], cardiac rupture may occur equally in any area of the left ventricle.

The surgical technique must be expeditious and simple. Infarctectomy has been performed with success [1, 4, 5, 7, 8] but involves extracorporeal circulation and suturing on an infarcted ventricle, a situation that can be dangerous and frustrating. Löfström and associates [22] reported a case where a Dacron patch was glued over the area of rupture but it loosened soon. Reinforcement of the sutures with strips of Teflon felt may prevent tearing, but the technique used by Nuñez and associates [9] of covering the area with a large patch and anchoring it to normal myocardium with continuous suture appears safer.

Our modification entails the use of a biocompatible glue. Cyanoacrylate is the basic component of the "super-glues" available for domestic use. Its main advantage is that does not require an activating substance because it polymerizes rapidly when in contact with water or tissue moisture. It comes in liquid form and has a much stronger adhesive capacity than other biological or biocompatible glues that are used mainly for sealant or reinforcement purposes [24, 25]. No toxic effects have been observed.

In our patients a large patch to enhance adhesion to the ventricular wall was applied over the area of rupture and fixed to the heart surface with a few drops of glue in each corner. With more drops over it, the patch became firmly adherent to the epicardium in less than 1 minute. Bleeding was stopped in all patients, and no recurrent hemorrhage appeared.

In summary, subacute cardiac rupture must be suspected in a patient recovering uneventfully of a transmural myocardial infarction in whom chest pain develops with sudden collapse and signs of cardiac tamponade. Surgical treatment must be initiated promptly. The use of a patch applied to the area of rupture and fixed to the heart surface by means of a strong surgical glue is a quick, effective, and safe method to deal with this lethal complication of myocardial infarction.

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DISCUSSION

DR FREDERICK A. CRAWFORD, JR (Charleston, SC): We have been interested in this particular technique for closing ventricular septal defects, and applied it in the experimental laboratory. It is true that the patch will stick to the heart, but the adherence seems to be relatively superficial so that you actually tear off layers of the patch. The glue does not come loose, but you simply tear off layers of the myocardium. What is it like when you do this; have you had that experience? Also, do you have any follow-up studies or anything to show whether you have any false aneurysms or anything of that type?

DR ARIS: Well, as I showed in the pictures of the procedure, once you have finished it, the whole thing is like a hard mass. It is almost impossible to tear it out, and we have not seen any detachment. In all patients there was complete control of the bleeding, although there was squirting of blood in only 2 patients. In the rest there was just an oozing.

We had a patient who was an airline pilot, and, for professional reasons, he (and, of course, the company) wanted to know how

his heart was. He had ruptured through an inferior infarct, and the angiogram performed several months later showed an occlusion of the right coronary artery as the only lesion. The rest of his coronary arteries were normal. The ventricular function was fairly good. Also we did echocardiograms in 7 patients, and in 3 we found saccular dilatation of the wall of the ventricle.

DR MOLIARI (New Haven, CT): What are the long-term results if further coronary artery disease develops in these patients and you need to do a reoperation on them? Would you be able to dissect the heart with all this glue attachment around?

DR ARIS: Regarding the long-term results, in 5 years we had only 2 patients with mild exertional angina. One is a very heavy, diabetic woman. In the patients who rupture, when you do an angiogram, as I pointed out, very often there is only one-vessel disease. That does not mean that you cannot have a patient with more than one diseased vessel, but in this case I do not think that

I would be able to go back to do a bypass graft in the area where the patch was glued.

DR CRAWFORD: Would you find this technique useful for a posterior left ventricular rupture after mitral valve replacement? Have you had a chance to use it for that?

DR ARIS: Yes. We did it in 1 patient who had a tear of the posterior wall of the left ventricle. We put on the glue and the bleeding was controlled, but it progressed to other areas. The patient eventually died and we did an autopsy. The pathologist had a hard time trying to detach the patch from the heart.

DR GUS J. VLAHAKES (Boston, MA): Does the material work in a field where there is still active bleeding? How do you get it to adhere to muscle where the bleeding may be rapid enough to wash it off?

DR ARIS: The glue is activated by moisture, so you need a little bit of the moisture of the tissues, but if there is active bleeding, very rapid, the glue does not have time enough to dry and it is washed off from the bleeding area.

DR WILLIAM I. BRENNER (Beverly Hills, CA): I want to congratulate the authors of this report on this excellent technique. I do not know if it is useable in the United States because of our Food and Drug Administration's restrictions on cyanoacrylate glue. I see you have the category of "blow-out leading to death." Occasionally the cardiac surgeon is unfortunate enough to be summoned to the catheterization laboratory for one of these "death" category patients. Do you have statistics on how many patients in this population were considered "dead" because they could not be subjected to this treatment?

DR ARIS: I do not have the exact numbers of patients who had an instant death during the 5 years that we have been using this technique, but that quite often happens, mainly if the patient has a blown-out rupture at 3 o'clock in the morning. You cannot get the surgical team to do the operation, even if you do not need extracorporeal circulation.

I just have one closing remark. We are aware, more than ever, that we do not cure the disease, we just stop the process. But we should keep in mind the saying by Charles Clavel, a French surgeon, who said: "Before we save the function, we must save the functionary."

Human Cryopreserved Homografts: Electron Microscopic Analysis of Cellular Injury

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Twenty-five human cryopreserved valves with harvest-related warm ischemic times (WITs) ranging from 0 to 20 hours were studied using transmission electron microscopy to characterize the effects of harvesting and preservation on leaflet matrix cells. The valves were divided into seven groups on the basis of WIT and processed using standard transmission electron microscopic methods. Each cell (528 micrographs) was graded for reversible and irreversible cellular injury and subjected to a Cochran-Mantel-Haenszel trend analysis. Our results demonstrated a progression in cellular injury with increasing WIT. During the first 12 hours of warm ischemia, reversible cellular injury predominated (0.0%, 30.0%, 51.2%, 31.3%, 35.1%, 45.1%, and 40.0% at WITs of 0, 1, 2, 8, 12, 16, and 20 hours, respectively). A positive correlation ($p < 0.0001$) between increasing WIT and reversible cellular injury through the first 12 hours was

observed. Minimal morphologic evidence of irreversible injury was noted in valves harvested with less than 12 hours of warm ischemia; however, after 12 hours there was a marked increase (0.0%, 0.0%, 4.7%, 2.4%, 2.7%, 31.4%, and 40.0% at WITs of 0, 1, 2, 8, 12, 16, and 20 hours, respectively) in irreversible cellular injury ($p < 0.001$ between 12 and 20 hours WIT). These data demonstrate a progression in cellular injury with increasing WIT. There was virtually no morphologic injury in valves with harvest-related WITs less than 2 hours and minimal irreversible cellular injury observed in valves exposed to 12 hours or less of warm ischemia. If cellular viability is critical to homograft durability then harvest-related warm ischemia may need to be restricted to 12 hours.

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Currently, there are three categories of prostheses available, with the selection of a specific replacement heart valve design being dictated by clinical indications, patient factors, and surgeons' preference. Although the ideal cardiac valve replacement has yet to be identified, the human cryopreserved homograft offers numerous clinical advantages for ventricular outflow reconstruction over both mechanical and xenograft valves: (1) relative resistance to endocarditis; (2) optimal hydraulic performance especially in the small aortic root size of children; (3) low incidence of thromboembolic complications; and (4) freedom from long-term anticoagulation and superior performance in the right ventricular outflow tract position [1]. Long-term durability of the homograft, although uncertain, seems to be influenced by the preimplantation processing method chosen (Fig 1). Historically,

the spectrum of these methods ranges from cold storage in nutrient media to treatment with aldehydes, antibiotics, or β -propiolactone to ethylene oxide and irradiation [3, 6]. Harsh chemical disinfection (ie, high concentrations of antibiotics, aldehydes, or β -propiolactone) and irradiation have been shown to reduce allograft durability [4, 6]. Homografts prepared by various gentle methods (ie, low-dose antibiotics) appear to have durability exceeding porcine, but perhaps less than mechanical valves [7-9]. Currently, homografts are disinfected using lower concentrations of antibiotics followed either by cryopreservation or storage of the valve in cold (4°C) nutrient media. There remains a paucity of data assessing the effects of procurement and processing on the morphologic integrity of the cryopreserved valve leaflets.

Current harvesting protocols are based on the premise that cellular viability enhances allograft durability [2, 10-16]. All valves harvested have an obligatory period of warm ischemic time from the death of the donor to immersion of the valve in cold storage solution. This obligatory warm ischemic time has been shown to affect matrix cell viability, but the time-dependent injury response has not been well characterized. Historically, valves have been harvested up to 72 hours after donor death. Most centers limit the warm ischemic time to less

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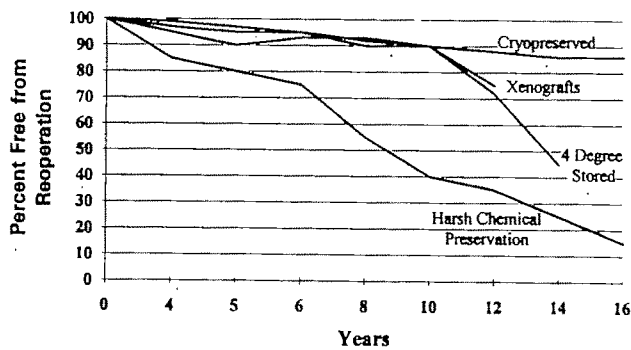


Fig 1. Comparison of the durability of homografts processed by cryopreservation (O'Brien and associates [2]), with storage in 4°C nutrient media (Barratt-Boyes and colleagues [3]), and using harsh chemical preservation methods (Daly and co-workers [4]). Also included is the expected durability of the xenograft valves (Spampinato and associates [5]).

than 24 hours, whereas others severely restrict harvest to only virtual beating heart donors.

The purpose of this study was to quantitatively characterize the combined consequences of variable warm ischemic injury, antibiotic disinfection, cryopreservation, and thawing on human leaflet matrix cell morphology using transmission electron microscopy.

Material and Methods

Study Design

Twenty-five human cryopreserved aortic and pulmonic valves with warm ischemic times ranging from 0 minutes to 20 hours were obtained (LifeNet Transplant Services, Virginia Beach, VA) and studied using transmission electron microscopy to characterize the effects of harvesting, antibiotic disinfection, and cryopreservation on leaflet matrix cell ultrastructure. Valves were acquired by means of a standard clinical procurement and cryopreservation protocol [17]. Homograft valves selected for study were rejected for transplantation for the following reasons: (1) positive bacterial cultures (18/25 valves); (2) thickened semilunar cusps or atheromatous plaques (3/25 valves); (3) technical error during valve harvest (3/25 valves); and (4) annular hematoma (1/25 valves). The valves were divided into seven groups on the basis of warm ischemic time: group 1, 0 minutes; group 2, 0 to 1 hour; group 3, 1 to 2 hours; group 4, 2 to 8 hours; group 5, 8 to 12 hours; group 6, 12 to 16 hours; and group 7, 16 to 20 hours. Two leaflets from each valve were randomly selected for study using standard transmission electron microscopic methods.

Valve Procurement and Preservation

All the valves were aseptically procured in an operating room and cryopreserved by LifeNet. The warm ischemic time from each valve was recorded and the valve transported (4°C) in either RPMI 1640 nutrient media, 0.9% saline solution, or lactated Ringer's to the tissue bank for processing [17]. Each homograft was cultured, excess myocardium and fat were removed, and the internal valve

diameter was determined. Subsequently, the homograft was disinfected in RPMI 1640 nutrient media-antibiotic solution (cefotaxime, 240 µg/mL medium; lincomycin, 120 µg/mL medium; polymyxin B, 100 µg/mL medium; and vancomycin, 50 µg/mL medium) at 4°C for 24 hours. The homografts were then cryopreserved (1°C per minute, 10% dimethyl sulfoxide) and stored in vapor liquid nitrogen (−150°C to −190°C). The homografts were initially thawed by immersion of the storage packet in a 40°C water bath for 10 minutes with subsequent stepwise dilution of the dimethyl sulfoxide cryoprotectant using increasing volumes of fresh RPMI 1640 nutrient media (dimethyl sulfoxide concentrations, 7.5%, 5.0%, 2.5%, and 0.0%). Two semilunar cusps from each valve were fixed using 1% glutaraldehyde + 4% formaldehyde in 0.1 mol/L phosphate buffer (pH 7.4).

Transmission Electron Microscopy

After fixation, each cusp was cut from the free edge to the base and embedded in epoxy resin. To ensure that the cells observed were representative of the population of cells from each leaflet, multiple thin sections from each tissue block were cut, and one thin section from each valve leaflet was randomly selected for morphologic observation. Transmission electron microscopic studies (80 kV; JEOL 100 CX transmission electron microscope, Tokyo, Japan) were conducted using standard methods [18]. The first ten cells observed in each thin section were photographed (20 photomicrographs per valve), and the extent of cellular injury was assessed using the following criteria: (1) reversible injury (cytoplasmic edema, dilation of the endoplasmic reticulum, mitochondrial swelling) and (2) irreversible injury (mitochondrial flocculent densities, karyolysis, and disruption of the plasma membrane).

Statistical Analysis

For this study, 528 photomicrographs were analyzed. A spreadsheet containing the valve identification and the results of our analysis was constructed (Quattro Pro 3.0, Borland, Santa Cruz, CA). These data were cross-tabulated, and the resulting contingency table was analyzed for a possible linear association between time and the number (percentage) of damaged cells. A Cochran-Mantel-Haenszel χ^2 test (PC-SAS PROC.FREQ; SAS Institute, Cary, NC) was used to identify a linear association between the rows and columns of the contingency table.

Results

Fibroblasts and myofibroblasts are the predominant cell components of the leaflet matrix [19]. Endothelial cells were occasionally observed; however, they appear to be more susceptible to the effects of warm ischemia (Fig 2). Quantitative studies of leaflet collagen bundle crimp [20] and proteoglycans were not addressed in this study. A gradual increase in the number of matrix cells demonstrating morphological evidence of cellular injury with increasing duration of warm ischemia was observed (Table 1; Fig 3). After 12 hours of warm ischemia, virtually two-thirds of

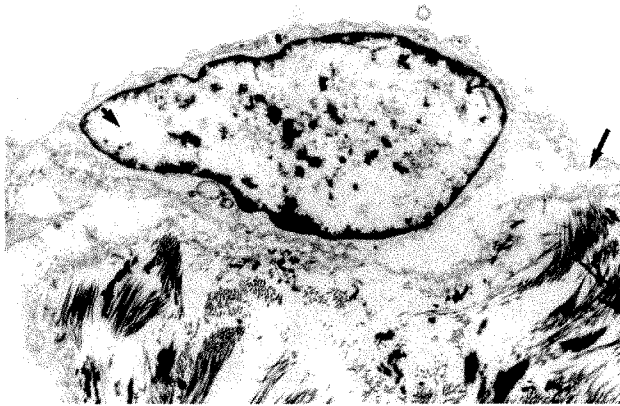


Fig 2. Irreversibly injured endothelial cell observed in a homograft exposed to 6 hours of warm ischemia, illustrating the sensitivity of this cell type to ischemic injury. Note the presence of karyolysis (short arrow) and loss of plasma membrane integrity (long arrow) (compare with Fig 4). (Uranyl acetate and lead citrate stain; $\times 5,400$ before 35% reduction.)

the leaflet matrix cells were morphologically unaltered (Fig 4). However, 20 hours of warm ischemia resulted in 80% of the cell population demonstrating evidence of cellular injury (Figs 5, 6). For the first 12 hours, injury was predominantly reversible with a positive correlation between reversible cellular injury and increasing warm ischemic time ($p < 0.0001$). Thereafter, irreversible injury was noted in an increasing proportion of cells (ie, 2.7% at 12 hours up to 40% at 20 hours). No irreversible injury was observed in any cells exposed to 1 hour or less of warm ischemia (ie, beating heart donors) followed by standard cryopreservation processing. There was a gradual increase in the number of irreversibly injured cells between 1 and 12 hours of warm ischemia; however, greater than 95% of cells were free of irreversible injury. A rapid increase in the number of irreversibly injured cells was noted when harvest-related warm ischemic times increased from 12 to 20 hours ($p < 0.001$). After 20 hours of warm ischemia 80% of the matrix cells demonstrated evidence of cellular injury (40% reversible, 40% irreversible). The alteration of matrix cell ultrastructural morphol-

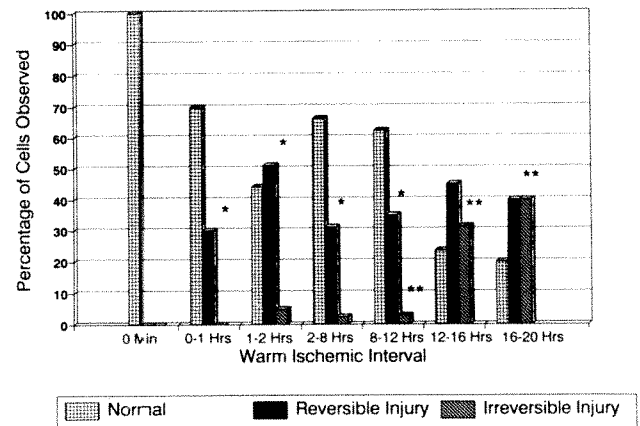


Fig 3. Percentage of cells observed in each category of cellular injury. X-axis groups represent the various warm ischemic intervals. Using a Cochran-Mantel-Haenszel trend analysis a positive correlation exists ($*p < 0.0001$) for reversible injury through the first 12 hours of warm ischemic time with a positive correlation ($**p < 0.001$) between 12 and 20 hours of warm ischemia for irreversible cellular injury.

ogy was observed in the following sequence: (1) dilation of endoplasmic reticulum; (2) cytoplasmic edema; (3) mitochondrial swelling; (4) presence of mitochondrial flocculent densities (ie, small, irregularly shaped electron-dense particles); (5) karyolysis; and (6) plasma membrane disruption.

Comment

The results of this study quantitatively describe the ultrastructural changes associated with variable warm ischemic injury followed by antibiotic disinfection and cryopreservation to leaflet matrix cells of human cryopreserved homograft valves. Our findings demonstrate a gradual increase in reversible cellular injury through the first 12 hours of warm ischemia; however, after 20 hours of warm ischemia, 80% of the matrix cells demonstrated morphologic evidence for either reversible or irreversible cell injury. Remarkably, these data further demonstrate little irreversible damage to the leaflet matrix cells when processing is preceded by less than 12 hours of harvest-

Table 1. Percentage of Reversible and Irreversible Cellular Injury in Cryopreserved Human Valves Processed for Use as Homografts

Result	0 Minutes	0-1 Hour	1-2 Hours	2-8 Hours	8-12 Hours	12-16 Hours	16-20 Hours
Normal	100.0% (20/20)	70.0% (14/20)	44.1% (38/86)	66.3% (110/166)	62.2% (46/74)	23.5% (24/102)	20.0% (12/60)
Reversible injury	0.0% ^a (0/20)	30.0% ^a (6/20)	51.2% ^a (44/86)	31.3% ^a (52/166)	35.1% ^a (26/74)	45.1% (46/102)	40.0% (24/60)
Irreversible injury	0.0% (0/20)	0.0% (0/20)	4.7% (4/86)	2.4% (4/166)	2.7% (2/74)	31.4% ^b (32/102)	40.0% ^b (24/60)

^a A positive correlation exists between increasing warm ischemia and reversible cellular injury ($p < 0.0001$ by Cochran-Mantel-Haenszel trend analysis).
^b A positive correlation exists between increasing warm ischemic time and irreversible cellular injury ($p < 0.001$ by Cochran-Mantel-Haenszel trend analysis).

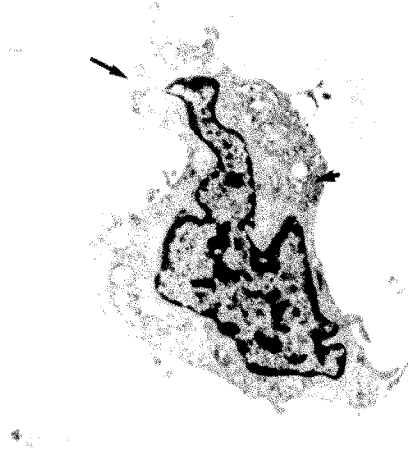


Fig 4. Representative micrograph depicts the ultrastructural features of an uninjured leaflet fibroblast after 6 hours of warm ischemia. Note the appearance of the nucleus (euchromatin, heterochromatin), mitochondria (long arrow), endoplasmic reticulum (short arrow), and cytoplasmic density. (Uranyl acetate and lead citrate stain; $\times 4,350$ before 35% reduction.)

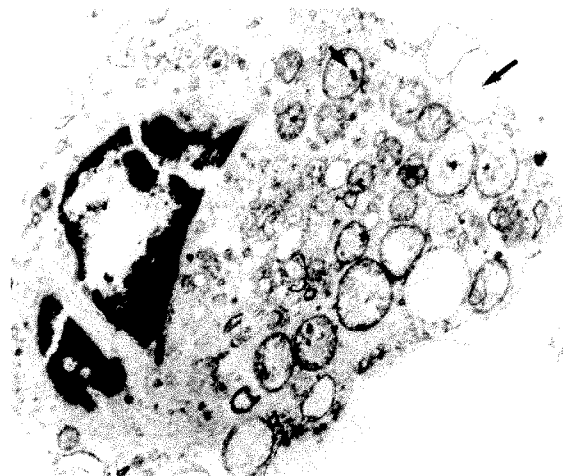


Fig 6. Higher magnification view of the cell depicted in Figure 4, demonstrating flocculent densities (short arrow) and dilation of endoplasmic reticulum (long arrow) after 20 hours of warm ischemia. (Uranyl acetate and lead citrate stain; $\times 10,500$ before 35% reduction.)

related ischemia; however, an additional 8 hours of warm ischemia greatly increases the number of cells that underwent irreversible cellular injury. Valves harvested with relatively short warm ischemic times (12 hours or less) contain a population of matrix cells in which the majority are morphologically unaltered and thus presumably will be viable after transplantation. The exact role of these fibroblasts in promoting homograft valve durability is currently speculative; it has been suggested that viable fibroblasts may facilitate the active renewal of extracellular components depleted as a consequence of harvesting, processing, valve implantation, and the dynamic leaflet motion during the cardiac cycle. Alternatively, the presence of viable leaflet fibroblasts may simply reflect gentle

preservation techniques and have little direct impact on the long-term durability of homografts.

Current harvesting and cryopreservation protocols are based on the premise that leaflet fibroblast viability enhances valve durability [2, 10-16]. Although this hypothesis has yet to be proved, this premise has gained acceptance by comparison with studies demonstrating the reduced durability of homografts processed by methods known to be toxic to leaflet matrix cells [4, 6]. Early attempts at increasing the shelf-life of banked homografts involved harsh preservation methods such as lyophilization, irradiation, and aldehyde pretreatment. The durability of homografts processed by these harsh methods is clearly inferior to that attained with present-day techniques, because 62% and 95% of patients required reoperation within 10 and 20 years of implantation, respectively [4]. In comparison, a 95% actuarial freedom from valve failure at 4 years and 92% at 10 years have been reported for cryopreserved homograft valves placed in the aortic position in adults [2]. Cold wet-stored homografts as reported by Barratt-Boyes and others (ie, a gentle technique with presumably low cellular viability) attain an actuarial freedom from valve replacement of 95%, 78%, and 42% after 5, 10, and 14 years of implantation, respectively [3]. The Brisbane experience with cold wet-stored homografts is similar, with 58% freedom from reoperation at 15 years [12]. Cryopreserved valves demonstrate a moderate advantage in terms of durability compared with cold wet-stored valves with a moderate increase in durability compared with porcine aortic valve xenografts in similar patient populations [7]. All homograft valves, regardless of processing and storage methods, demonstrate increased durability and performance in the right ventricular outflow tract as compared with xenograft valves [7, 21-23].

Harvest-associated warm ischemia may be a critical

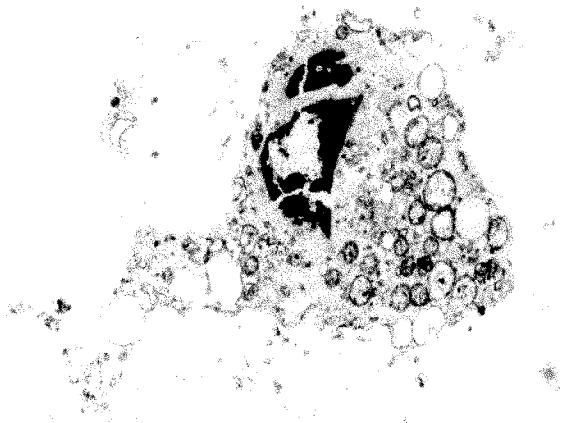


Fig 5. Severely injured leaflet fibroblast after 20 hours of warm ischemia, demonstrating extensive dilation of endoplasmic reticulum and mitochondrial flocculent densities. (Uranyl acetate and lead citrate stain; $\times 5,400$ before 35% reduction.)

determinant of fibroblast viability. Previous laboratory studies in which porcine aortic valves were harvested and exposed to variable periods of warm ischemia demonstrated a resilience by leaflet fibroblasts to the effects of warm ischemic injury for more than 24 hours [19] when studied before antibiotic disinfection and cryopreservation (ie, analogous to the time of cadaveric harvest-related ischemia). However, after 24 hours of warm ischemia a marked increase in the number of irreversibly injured cells was observed. A positive correlation between increasing warm ischemic time and irreversible cellular injury was demonstrated through 36 hours of warm ischemia. In the present study of human cryopreserved valves, our findings indicate the window of minimal warm ischemic injury is shorter (ie, 12 hours) before there is a marked increase in the number of irreversibly injured cells in leaflet tissue that has been harvested, processed, cryopreserved, and thawed in a manner analogous to current clinical protocols. This observation suggests that an additional reduction in the number of viable leaflet fibroblasts occurs when cadaveric harvest ischemia is followed by antibiotic disinfection, cryopreservation, and thawing. The animal studies are an important complement to understanding these human results, because the limited availability of donor tissue mandates full processing and clinical use of all human valves except for those found to be nontransplantable. Thus a control series for human valves that have only experienced cadaveric harvest ischemia is not available in this country.

The mechanism that renders the matrix cells susceptible to destruction may be related to depletion of high-energy phosphate intermediates during the warm ischemic interval. In an analysis of human cryopreserved valves processed for use as homografts, adenosine triphosphate levels decreased from 0.127 nmol/mg protein after 2 hours of warm ischemia to complete depletion of adenosine triphosphate after 13 hours of warm ischemia [24]. Significant reductions in adenosine triphosphate levels have also been observed in porcine aortic valves after brief periods of warm ischemia, antibiotic disinfection, and cryopreservation [25]. Furthermore, as the warm ischemic interval is increased, reductions in the levels of other adenine nucleotides (ie, adenosine diphosphate and adenosine monophosphate) occurs [26]. Accumulation of lactate in valvular tissue has been measured after 2 hours of warm ischemia, suggesting that around this time, ischemic leaflet cells have converted from aerobic to anaerobic metabolism [27]. Teleologically, cellular injury should progressively increase as metabolic reserves are further depleted during subsequent processing steps (ie, antibiotic disinfection, cryopreservation, and thawing) even if these steps are by themselves not toxic. Our morphologic observations in clinical human cryopreserved aortic homografts support these biochemical findings. Within relatively short periods of warm ischemia (1 to 12 hours), we observed evidence of reversible cellular injury (ie, cytoplasmic and mitochondrial edema, dilation of the endoplasmic reticulum). However, marked morphological evidence of irreversible cellular injury (ie, mitochondrial flocculent densities, karyolysis, plasma

membrane disruption) was not observed until after 12 hours of warm ischemia. These findings suggest that periods of warm ischemia less than 12 hours may represent the optimal window for valve procurement.

This study demonstrates that after 20 hours of warm ischemia and subsequent disinfection and cryopreservation 40% of the matrix cells in cryopreserved valves have been irreversibly injured. Morphologic criteria for reversible cellular injury (ie, cytoplasmic edema, dilated endoplasmic reticulum, swelling of the mitochondria) represent observations consistent with an inability of the cells to maintain osmotic gradients. With restoration of the metabolic reserves it is expected that these findings may regress. The markers of irreversible cellular injury (ie, mitochondrial flocculent densities, karyolysis, plasma membrane disruption) represent extensive cellular destruction with no chance of salvage. Mitochondrial flocculent densities, which are electron-dense irregularly shaped particles composed of calcium and phosphate found within the mitochondria matrix, correspond to the biochemical uncoupling of oxidative phosphorylation. Their presence may signal irreversible mitochondrial damage and severe depletion of intracellular adenosine triphosphate.

Results of this morphologic study demonstrate a marked increase in matrix cell irreversible injury after harvest-related warm ischemia greater than 12 hours in human allografts processed as clinical quality homograft valves. Previously, worldwide harvesting protocols allowed widely variable cadaveric harvests up to 72 hours postmortem, but currently, most restrict harvest to within 24 hours. If fibroblast viability is a significant determinant of homograft durability and performance, then warm ischemic time associated with valve procurement should be restricted to 12 hours or less unless modifications of processing methods can be implemented that reverse the progression of injury. Limiting harvests to beating heart donors is probably too restrictive and is not supported by our data. Unlike myocardial cells, fibroblasts are remarkably resilient and do not die within minutes after the onset of ischemia. Minimal cellular damage observed after short periods of cadaveric ischemia, cold antibiotic disinfection, and cryopreservation is quite impressive. Intuitively, one would expect negative effects of such processing; cryopreservation, as currently performed, is a standardized method extraordinarily effective in preserving the viability of previously uninjured valve leaflet cells. Cardiac surgeons should understand the implications of preprocessing warm ischemia and be aware of that time interval when selecting a cryopreserved homograft for transplantation, especially when prolonged durability is an issue for a specific patient. Currently our findings support three (conceptual) categories of cryopreserved homograft valves: (1) beating heart or virtual beating heart donors (less than 2 hours of warm ischemia); (2) short cadaveric harvest ischemia (2 to 12 hours); and (3) prolonged cadaveric ischemia (>12 hours but $\leq$ 24 hours). The matrix cell population in valves harvested more than 24 hours after donor death are almost certainly either nonviable or irreversibly injured, especially once exposed

to the rigors of preimplantation processing and transplantation.

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DISCUSSION

MR ENDRE BODNAR (Pinner, United Kingdom): I would like to congratulate Dr Crescenzo and associates. I hope that this excellent report will be published and quoted in relevant publications for many years to come because it clarifies a number of problematic issues. I would like to make a few comments.

First of all, this report seemed to prove what we have been believing for some time, that all of those homografts that have been implanted over the past 25 years were nonviable because they were harvested from cadavers 24 to 72 hours after death. One may conclude this from Crescenzo and associates' data.

The second thing I would like to comment on is that it may be a mistake to equate cryopreservation with viability. The Mark O'Brien series that you have used here as an example was a

mortuary series. Therefore, in light of your results, they were cryopreserved but nonviable valves. We presented to this Society a couple of years ago results obtained in London over a 20-year period in which there was no difference in clinical performance whether the homografts were believed to be viable or not.

As far as fibroblast viability is concerned, I would like to note that it does not mean that the valve is normal. First of all, a normal valve has endothelium, and fibroblasts do not produce endothelium. Neither do they produce elastin or collagen. They produce only procollagen, and a normal extracellular environment is necessary to turn it into collagen. The so-called viable valves are not normal, and there is a question as to whether the life of a fibroblast will extend the life of the homograft.

Finally, with a view to this, there may be a new evaluation of the truly viable valves. They may be much more antigenic than those homografts that we have been working with over the past 25 years, as acute rejection was a totally unknown complication of homograft insertion until these truly and highly viable valves arrived. So when you are proposing that the best valve should be given to the best patient, I would raise the question, which is the best valve? I am not sure that the most viable is the best.

DR CRESCENZO: Thank you very much for your comments. I would like to address several points in response to your remarks.

First, endothelial cells have never been shown to be important in terms of valve durability. In fact, preservation of endothelial cells may reduce valve durability by an immunologic mediated response. It has been shown that the immunologic reaction is a result of class I antigens expressed on the surface of the endothelial cells.

As far as our statements concerning the different categories of cryopreserved valves, we still have not been able to fully elucidate the exact role of the fibroblast in promoting valve durability. We do know that cryopreservation has been shown to preserve cellular viability; however, what may be more important in terms of valve durability is that cryopreservation causes less damage to the acellular components, and this is the reason that cryopreserved valves perform better than the harsh preservation series published by the Mayo Clinic.

DR PETER K. SMITH (Durham, NC): How would you handle the bias that is introduced into your data by the fact that such a large proportion of the valves were rejected because of positive cultures? We all understand that they have been warm ischemic in a medium that is conducive to this. To what extent do your data support your conclusions even in the remaining 8 or so that were not infected?

DR CRESCENZO: Dr Smith, thank you very much for your comments as well. This very question has been raised by members of our research team. The morphologic observations reported in this study were performed on human cryopreserved valves that were processed on line in a commercial distribution center. These valves were later rejected for transplantation because of technical reasons such as positive bacterial cultures. These were "technical" infections by virtue of positive surveillance cultures—not invasive infections causing thickened cusps, for example. If we assume a worse-case scenario, our data would be overreporting cellular injury, and I think you would agree that valves with warm ischemic times of less than 12 hours had remarkably little injury.

DR FLAVIAN M. LUPINETTI (Ann Arbor, MI): I enjoyed your report very much. I think it is very important to attempt to quantitate the quality of "viability," which is sometimes referred to rather loosely. But I wonder whether your methods really determine fibroblast viability as opposed to cell death; they may not be opposite sides of the same coin. Do you have any data that relate your histologic grading to proline uptake or autoradiography or some other more affirmative line of evidence that would indicate cellular viability?

DR CRESCENZO: The proline and inulin uptake studies have been done at Old Dominion University by Dr Wolfenbarger. Our morphologic observations correlate with his findings. Recently, our laboratory has been able to culture fibroblasts in porcine heart valves with warm ischemic time as long as 48 hours. We are currently looking at whether these fibroblasts can secrete collagen in a normal fashion. Our preliminary results demonstrate that fibroblasts will proliferate in cell culture, but we still do not know if these cells will function normally.

Warm Blood Cardioplegia: Superior Protection After Acute Myocardial Ischemia

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Three myocardial protection techniques were studied in a canine model of acute myocardial ischemia with subsequent revascularization. Eighteen animals were randomly assigned to one of three treatment regimens: cold oxygenated crystalloid cardioplegia (CC), cold blood cardioplegia with modified reperfusate (CB), and continuous aerobic warm blood cardioplegia (WB) ($n = 6$ per group). Systemic hypothermic cardiopulmonary bypass (28°C), antegrade arrest, and intermittent retrograde and antegrade delivery were used for the CC and CB groups. Systemic normothermic cardiopulmonary bypass, antegrade arrest, and continuous retrograde delivery were used for the WB group. Fifteen minutes of warm global ischemia was followed by occlusion of the left anterior descending coronary artery (15-minute duration) and simultaneous initiation of cardioplegic arrest (60-minute duration) to simulate clinical revascularization. After reperfusion, the animals were separated from cardiopulmonary bypass. Myocardial function, electrocardiogram, myocardial energetics, water content, histopathology, and defibrillation requirements were compared between

groups. There was no significant difference in maximum elastance, myocardial oxygen consumption, myocardial edema, or histopathologic evidence of injury between groups. However, overall ventricular function, assessed by the slope of the preload recruitable stroke work relationship, was significantly better for the WB group ($p = 0.04$) (WB, 73 ± 9 ; CB, 56 ± 7 ; CC, 47 ± 5). Diastolic function as assessed by the slope of the stress-strain relationship was significantly worse overall for the cold groups ($p = 0.001$) (WB, 20 ± 2.2 ; CB, 39 ± 1.3 ; CC, 37 ± 3.1). Myocardial injury as assessed by ST segment elevation (millimeters) was less for the WB group ($p = 0.03$) (WB, 0.4 ± 0.3 ; CB, 1.7 ± 0.2 ; CC, 1.6 ± 0.7). Counter-shocks necessary to restore sinus rhythm after cross-clamp removal were fewer in the WB group ($p = 0.03$) (WB, 0.8 ± 0.3 ; CB, 4.0 ± 1.2 ; CC, 5.5 ± 1.5). In this model of acute global myocardial ischemia, continuous aerobic warm blood cardioplegia has important advantages over two widely used clinical hypothermic protection techniques.

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Modern hypothermic cardioplegic myocardial protection techniques as practiced by the majority of cardiac surgeons yield excellent functional results. Most cardiac operations are carried out well within the bounds of safe limits of these techniques. There are certain important subsets of patients, however, that stretch these margins of safety. Patients with acute myocardial ischemia, those requiring extended cardiac arrest time for repair of complex problems, and patients with minimal myocardial functional reserve are particular challenges to existing hypothermic ischemic cardioplegic arrest techniques.

A new myocardial protection technique that uses aerobic warm blood cardioplegia, developed by surgeons at the University of Toronto, has shown promise in recent clinical studies of these problem patients [1-3]. To assess quantitatively the functional results with this new technique,

a comparison was made between aerobic warm blood cardioplegia and two clinical state-of-the-art cold cardioplegic techniques in a canine model of acute myocardial ischemia. Experimental end points included assessments of cardiac mechanics, cardiac energetics, myocardial edema, and histopathologic and electrocardiographic changes.

Material and Methods

Eighteen *Dirofilaria*-free adult mongrel dogs with body masses ranging from 23 to 32 kg were studied in a right heart bypass model of acute myocardial ischemia with simulated revascularization. All animals were premedicated with morphine sulfate (4 mg/kg) subcutaneously. Anesthesia was induced with intravenous administration of sodium pentobarbital (20 mg/kg) and maintained with intermittent boluses (3 mg/kg). The animals were endotracheally intubated and placed on a volume ventilator. Femoral artery pressure was monitored. Limb leads were placed for recording the electrocardiogram. A median sternotomy allowed cannulation of the left subclavian artery for inflow from the cardiopulmonary bypass (CPB) circuit. Venous return to the pump was through bicaval

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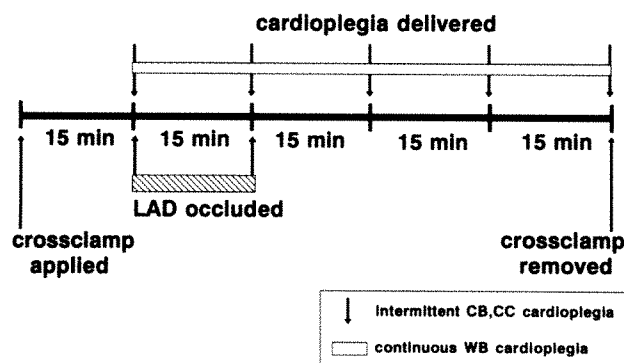


Fig 1. Time line of experimental model. (CB = cold blood cardioplegia; CC = cold crystalloid cardioplegia; LAD = left anterior descending coronary artery; WB = warm blood cardioplegia.)

cannulation. The animals were initially placed on normothermic total CPB. The azygos vein was ligated. An ascending aortic cardioplegia delivery cannula was placed and secured.

Global myocardial ischemia was then initiated by cross-clamping the ascending aorta to eliminate coronary arterial flow (Fig 1). Warm myocardial ischemia was maintained for 15 minutes. During this time, the left ventricle was passively vented through the apex. The left anterior descending coronary artery (LAD) was mobilized and an encircling tourniquet placed just distal to the first septal perforator. At this point, one of the three myocardial

protection regimens was initiated (Table 1). If the animal received a cold cardioplegic technique (cold blood cardioplegia [CB], cold crystalloid cardioplegia [CC]), systemic cooling to 28°C was initiated. The group given warm blood cardioplegia (WB) had maintenance of systemic normothermia throughout. The LAD tourniquet was released 15 minutes after initiation of the cardioplegic regimen in each group, simulating surgical revascularization.

During cardiac arrest, the tricuspid valve was rendered incompetent, and a right atrial drainage line was placed to collect coronary sinus and thebesian effluent. During the subsequent working phase, this flow was returned to the pump and quantitated by electromagnetic flowmetry and intermittently sampled for oximetric analysis. Also during the arrest phase, the left ventricle was instrumented for pressure-volume studies with a high-fidelity micromanometer and three pairs of orthogonally oriented endocardial-surface ultrasonic pulse transit crystals [4].

The animals that had been systemically cooled were rewarmed to systemic normothermia. The cross-clamp was removed 75 minutes after initial placement. The heart was reperfused at a mean aortic pressure of 50 mm Hg for 2 minutes, after which the pressure was raised to 70 mm Hg where it was maintained for the remainder of the experiment. Direct-current defibrillation was ultimately successful for those hearts that did not resume a spontaneous organized rhythm. Boluses of lidocaine hydrochloride (1 mg/kg) were administered to all animals after two unsuccessful defibrillation attempts. Serum po-

Table 1. Characteristics of the Three Myocardial Protection Regimens

Group	Induction Dose		Induction Solution	Maintenance Dose	Maintenance Solution	Terminal Reperfusate	Systemic Temperature (°C)	Topical Cooling
	Antegrade	Retrograde						
CC	20 mL/kg, 4°C	10 mL/kg, 4°C	1 L solution: 20 mEq/L HCO ₃ ⁻ ; D ₅ W, 3 mL/L; KCl, 20 mEq/L; Na, 141 mEq/L; Mg, 3 mEq/L; Cl, 98 mEq/L; Acetate, 27 mEq/L; Phosphate, 1 mEq/L; Gluconate, 23 mEq/L; pH, 7.4	15 mL/kg, intermittent (q 15 min), antegrade	Same solution	No	28	Yes
CB	20 mL/kg, 4°C	10 mL/kg, 4°C	1 part crystalloid solution: D ₅ ¼ NS, 750 mL; KCl, 80 mEq/L; THAM, 200 mL; CPD, 200 mL; 4 parts blood	15 mL/kg, intermittent (q 15 min), antegrade	1 part same solution except KCl, 20 mEq/L; 4 parts blood	Yes ^a	28	Yes
WB	20 mL/kg, 37°C	Continuous, 37°C, CSP-40 mm Hg	1 part crystalloid solution: D ₅ W, 1 L; KCl, 100 mEq/L; Mg, 18 mEq/L; THAM, 40 mL; CPD, 20 mL; 4 parts blood	Continuous, retrograde	1 part same solution except KCl, 40 mEq/L; 4 parts blood	No	37	No

^a The terminal reperfusate was given as an antegrade dose, 15 mL/kg, just before cross-clamp removal. The composition was as follows: D₅W, 250 mL; D₅W, 40 mL; CPD, 225 mL; THAM, 225 mL; KCl, 30 mEq/L; glutamate/aspartate solution, 250 mL (2.02 g aspartate + 2.20 g glutamate per liter of D₅W).

CB = cold blood cardioplegia; CC = cold crystalloid cardioplegia; CPD = citrate-phosphate-dextrose; CSP = coronary sinus pressure; D₅W = 5% dextrose in water; D₅¼ NS = 5% dextrose in 0.25% normal saline solution; THAM = trihydroxymethylaminomethane; WB = warm blood cardioplegia.

tassium concentrations were maintained between 3.5 and 5.5 mmol/L (3.5 and 5.5 mEq/L) throughout the protocol.

For 20 minutes after cross-clamp removal, the hearts were kept in a vented nonworking state on CPB. The left ventricular working phase was begun by infusing blood into the main pulmonary artery at $75 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. Data were gathered during 10-minute working phases at 30, 60, and 90 minutes after cross-clamp removal. Between these data collection periods, the animals were kept on CPB.

All animals received humane care in compliance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research and the "Guide for the Care and Use of Laboratory Animals" prepared by the National Academy of Sciences and published by the National Institutes of Health (NIH publication No. 85-23, revised 1985).

Data Acquisition and Analysis

Hemodynamic data were gathered using an analog-to-digital conversion board (Data Translation, Inc, Marlboro, MA) and processed, stored, and analyzed with a micro-processor (model 386; Intel, Houston, TX) using an interactive program developed in this laboratory (James M. Bradford, PhD; © Emory University, 1991). The system was formatted to collect 6-second recordings of 16 channels of physiologic data. Channels were sampled every 4 milliseconds with a delay between channels of 0.25 milliseconds (250 Hz per channel). The program generated pressure-volume loops from the left ventricular micromanometer and the triaxially arrayed ultrasonic crystal dimension data as previously described from this laboratory [4].

Systolic ventricular performance was evaluated by determining the slope of the maximum elastance or end-systolic pressure-volume relationship (E_{max}) from the 6-second periods of data collection acquired during varying preload conditions [4, 5]. For the computations, the program was formatted such that end-systole was defined as the point when the pressure-volume ratio was at a maximum.

Diastolic function was assessed by calculating both left ventricular midwall circumferential stress and left ventricular Lagrangian volume strain (see Appendix 1 for derivation of the formulas used to calculate these values). End-diastole was defined as the point 32 milliseconds before the time at which the slope of the left ventricular pressure curve exceeded 1. The interactive features of the program allowed visual confirmation of the validity of these points. End-diastolic points from successive cardiac cycles during a 6-second period of rapidly changing preload minimized problems with consideration of parallel viscous properties [6]. These calculated values for stress and strain were then pooled into a single set of data points for each group and analyzed by general linear modeling and analysis of covariance for the presence of a group effect.

Overall ventricular performance was quantitated and evaluated by determining the linearized Frank-Starling relationship. This preload recruitable stroke work (PRSW)

relationship was obtained by computer integration of the area within the left ventricular pressure-volume loops. The area for a given cardiac cycle was plotted against the left ventricular end-diastolic volume for that cycle. The PRSW line was obtained as a least squares regression of multiple cardiac cycles during acute variation of the preload [4, 7].

Electrocardiographic data were collected with limb leads. Lead II was calibrated for 1 mV equal to 10 mm.

Myocardial oxygen consumption (MVO_2) was calculated using the formula:

$$\text{MVO}_2 \text{ HEART} = (C_a - C_v) \times Q,$$

where Q was the coronary blood flow quantitated by electromagnetic flow probe determination of the combined coronary sinus and thebesian vein effluent, C_a was the arterial oxygen content determined from a sample drawn from the arterial line of the CPB circuit and analyzed with an oximeter that was calibrated for canine hemoglobin to determine oxygen content (model OSM3; Radiometer, Westlake, OH), and C_v was the venous oxygen content determined from a simultaneous sample drawn from the combined coronary sinus and thebesian vein effluent. Samples were drawn at 5-minute intervals after cross-clamp removal until the completion of the experiment.

The right ventricle remained in the nonworking state throughout the postreperfusion course of the experiment. An assumption was made that the nonworking right ventricular MVO_2 ($\text{MVO}_2 \text{ RV NW}$) remained constant. Another assumption was that the atria consumed oxygen in proportion to their weight and that this remained constant. This nonworking right ventricular and atrial (A) oxygen consumption was calculated during the nonworking phase immediately before each working-phase MVO_2 measurement by the formula:

$$\text{MVO}_2 \text{ RV A NW} = \text{MVO}_2 \text{ HEART} \times [(\text{RV mass} + \text{A mass})/(\text{RV mass} + \text{A mass} + \text{LV mass})],$$

where LV mass was left ventricular mass, RV mass was right ventricular mass, and A mass was the combined atrial mass determined by the postmortem weight of the ventricles and atria stripped of the valvular apparatus, great vessels, and atrioventricular fat pad. The septum remained with the left ventricle.

Left ventricular oxygen consumption ($\text{MVO}_2 \text{ LV}$) was calculated by the formula:

$$\text{MVO}_2 \text{ LV} = \text{MVO}_2 \text{ HEART} - \text{MVO}_2 \text{ RV A NW}.$$

The $\text{MVO}_2 \text{ LV}$ was then normalized to 100 g of left ventricular mass:

$$\text{MVO}_2 \text{ NORMAL} = [\text{MVO}_2 \text{ LV}/\text{LV mass}] \times 100.$$

Normalized values were compared between groups in both the working and nonworking phases.

Myocardial water content was determined from samples of the left ventricle taken immediately after death, weighed, and placed in an oven for desiccation. The

samples were weighed daily until a constant weight was obtained for 2 days. The percent water content of the tissue was determined by the equation:

$$\text{Tissue \% water content} = \frac{[(\text{wet weight} - \text{dry weight})/\text{wet weight}] \times 100}{1}$$

Histologic examination was performed on transmural sections of the left ventricle taken from the LAD and circumflex coronary artery areas away from areas of instrumentation. These were then fixed in 10% buffered formalin. Sections were stained with hematoxylin and eosin and examined by a pathologist. Microscopic examination was carried out using high-power (40× objective, 10× ocular) fields. Each field examined was scored yes or no for the presence of one of the following markers of myocyte damage: contraction band necrosis, hyper eosinophilia, or smudging of the myofibrils with loss of cytoplasmic detail (poorly visible cross striations). The score for a particular sample was the ratio of fields exhibiting at least one of the markers of damage to the total number of fields examined (range of fields examined, 73 to 134). Specimens were also evaluated for presence and severity of intramyocardial hemorrhage for both the LAD and circumflex regions. The scoring system was as follows: 0 = no evidence of intramyocardial hemorrhage; 1 = one to three foci of hemorrhage in either the LAD or circumflex area only; 2 = one to three foci of hemorrhage in both regions; 3 = extensive hemorrhage in one region, and 4 = extensive hemorrhage in both regions.

Statistical Analysis

Statistical analyses were carried out on a microprocessor using proprietary software (RS1, BBN Software Products Corp; BMDP, BMDP Statistical Software, Inc) with the advice of a statistician (R. S. Clark, PhD, Emory University). Myocardial water content, histologic injury scores, and defibrillation requirements were compared using one-way analysis of variance. Intramyocardial hemorrhage scores were compared using χ^2 testing. Diastolic stress-strain data were compared by analysis of covariance. All other comparisons were done by analysis of variance with repeated measures. All values are expressed as the mean $\pm$ the standard error of the mean. Significant differences were said to exist when the *p* value was less than 0.05.

Results

All animals were tapered from CPB. In general, the WB-protected animals had fewer rhythm disturbances and were separated more readily from bypass. The mean arterial pressure was maintained at 70 mm Hg (± 3 mm Hg), and the average heart rate was 166 beats per minute at the time of data collection. Left ventricular distention was assiduously avoided, and end-diastolic pressure did not exceed 15 mm Hg in any animal.

Ventricular systolic performance, assessed using the maximum elastance relationship ($E_{\max}$), showed no significant difference between groups (30 minutes—WB, 8.5

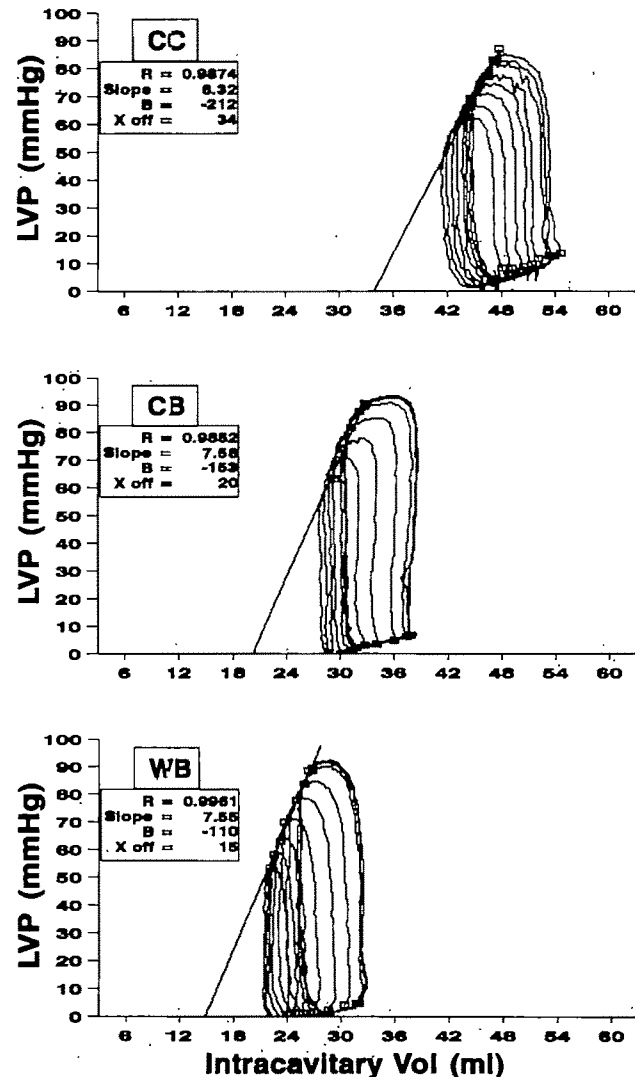


Fig 2. Typical pressure-volume loops from each group during varying preload conditions. Linear regression fitting of the maximum elastance relation ($E_{\max}$) is shown. Note also the steeper slope during diastolic filling characteristic of the cold protection groups compared with the more compliant aerobic warm protection group. (B = y-intercept; CB = cold blood cardioplegia; CC = cold crystalloid cardioplegia; LVP = left ventricular pressure; R = correlation coefficient; WB = warm blood cardioplegia; X off = x-intercept.)

± 1.2 ; CB, 7.1 ± 1.6 ; CC, 6.0 ± 0.9 ; 60 minutes—WB, 11.5 ± 2.3 ; CB, 10.5 ± 2.0 ; CC, 7.0 ± 1.2 ; 90 minutes—WB, 10.1 ± 1.6 ; CB, 9.3 ± 1.5 ; CC, 7.2 ± 2.0); however, the mean slope was greater for the WB group at all times (Figs 2, 3). The mean correlation coefficient for the $E_{\max}$ linear regressions was 0.98.

Analysis of diastolic function, as evaluated by the stress-strain relationship, revealed significantly diminished ventricular compliance in the cold groups. The slope of the stress-strain relationship was significantly lower in the WB group compared with the cold groups ($p = 0.001$) (WB, 20 ± 2.2 ; CB, 39 ± 1.3 ; CC, 37 ± 3.1) (Figs 4, 5).

Overall left ventricular performance, as assessed by the

PRSW relationship, was significantly better for the WB group at all times ($p = 0.04$) (Fig 6). Also, the CB group was significantly better than the CC group overall ($p = 0.04$) (CB, 66 ± 7 ; CC, 49 ± 7). There was improvement in overall ventricular function for the CB group over time ($p = 0.008$) (30 minutes, 56 ± 6 ; 90 minutes, 73 ± 9). The WB and CC groups, however, did not demonstrate this time effect (WB: 30 minutes, 73 ± 9 ; 90 minutes, 82 ± 7 ; CC: 30 minutes 47 ± 5 ; 90 minutes, 55 ± 5 ; $p =$ not significant). The mean correlation coefficient for the PRSW relationship was 0.98.

Electrocardiographic analysis demonstrated significant ST segment elevation that persisted across time in both cold cardioplegic groups ($p = 0.03$) (Fig 7).

Myocardial oxygen consumption was used to assess cardiac energetics. There were no significant differences in MVO_2 between groups either early after cross-clamp removal during the nonworking phase or over time (Fig 8).

There were also no significant differences in the postoperative percent myocardial water content between groups (WB, $77\% \pm 2\%$; CB, $77\% \pm 1\%$; CC, $78\% \pm 1\%$).

Histologic examination showed presence of myocardial damage in all three treatment groups; however, there was

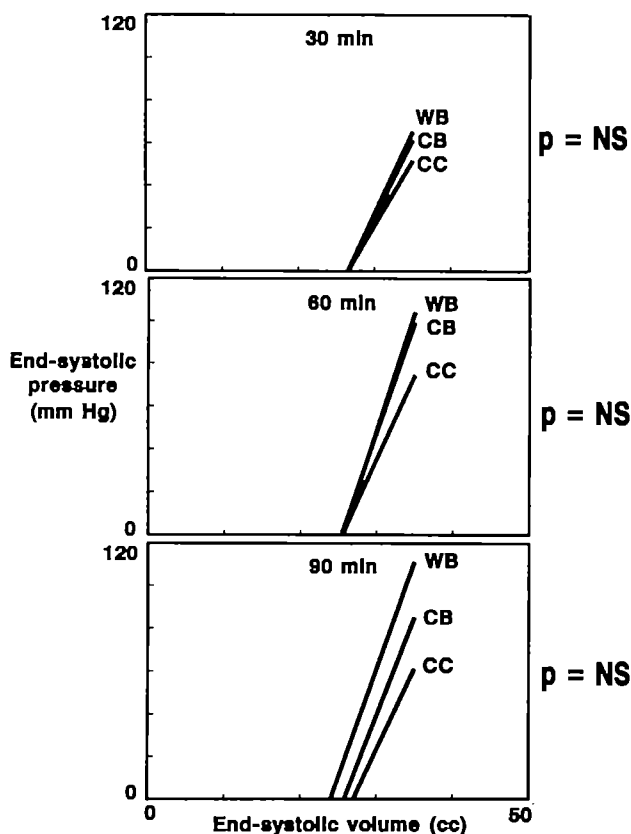


Fig 3. Comparison of systolic myocardial performance using the mean slopes and intercepts of the maximum elastance relationship (E_{max}) for each group during the working phase 30, 60, and 90 minutes after cross-clamp removal. (CB = cold blood cardioplegia; CC = cold crystalloid cardioplegia; NS = not significant at the $p < 0.05$ level; WB = warm blood cardioplegia.)

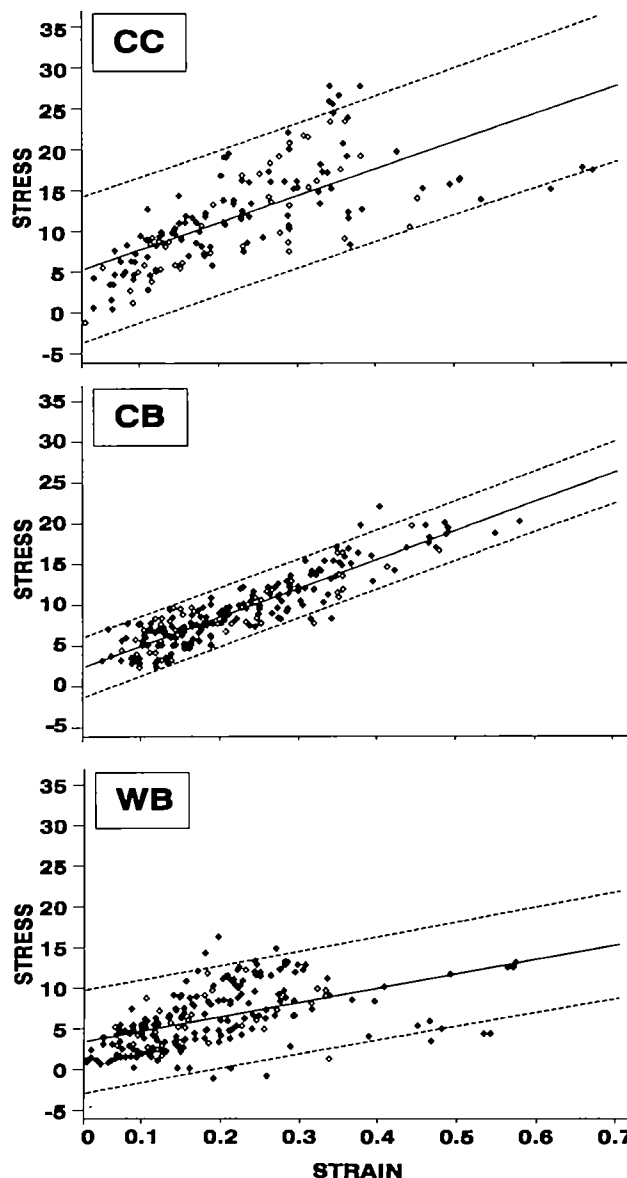


Fig 4. Pooled diastolic stress-strain raw data with linear regression fitting for each group during varying preload conditions (stress expressed as dynes $\times 10^3/\text{cm}^2$). (CB = cold blood cardioplegia; CC = cold crystalloid cardioplegia; WB = warm blood cardioplegia.)

no significant difference in the myocardial injury score between the two regions or between the three groups (combined LAD and circumflex scores: WB, 13.7 ± 2.1 ; CB, 7.9 ± 2.1 ; CC, 14.0 ± 4.7). There was also no difference in the intramyocardial hemorrhage score between the three groups (WB, 2.8 ± 0.6 ; CB, 2.8 ± 0.4 ; CC, 3.0 ± 0.3).

The number of countershocks necessary to resume sinus rhythm after cross-clamp removal was significantly less in the WB group (WB, 0.8 ± 0.3 ; CB, 4.0 ± 1.2 ; CC, 5.5 ± 1.5 ; $p = 0.03$).

Comment

Hypothermic cardioplegic techniques have been a mainstay for intraoperative myocardial protection for most

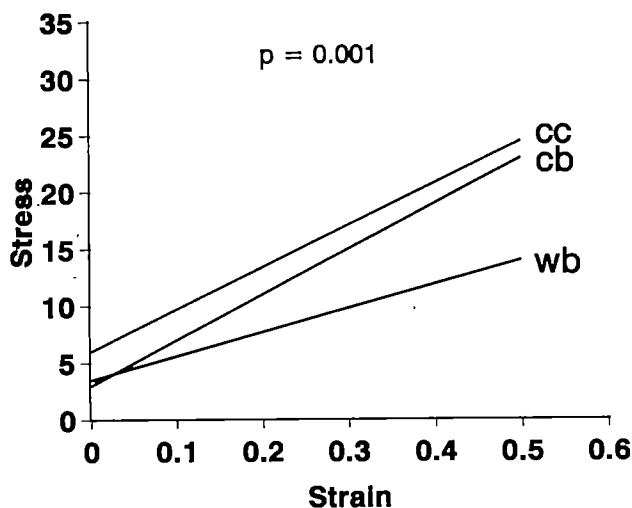


Fig 5. Comparison of diastolic stress-strain relationship between the three groups demonstrating the significantly more compliant left ventricle after aerobic warm blood cardioplegia (wb). (cb = cold blood cardioplegia; cc = cold crystalloid cardioplegia.)

cardiac surgeons. Central to these techniques is the profound change in myocardial oxygen and substrate delivery during the cross-clamp period and the use of chemical

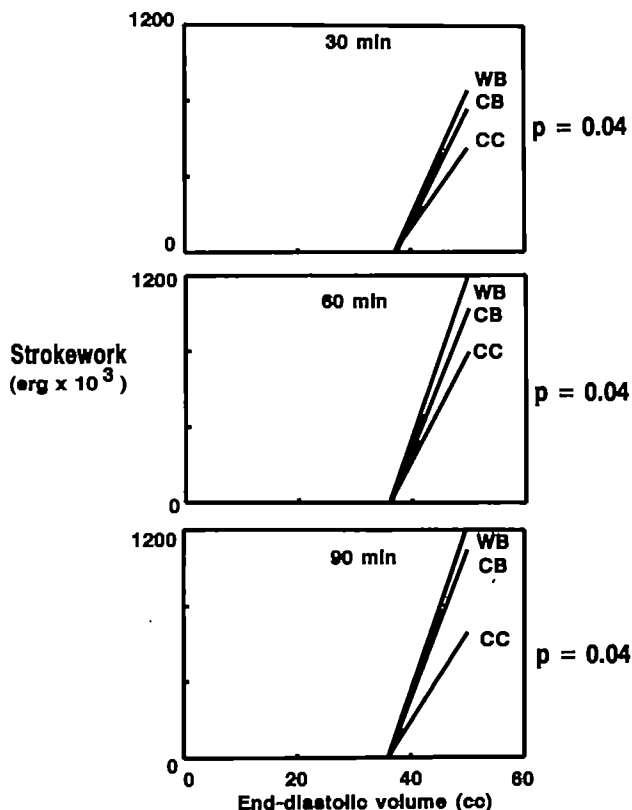


Fig 6. Global myocardial performance between groups quantitated by the preload recruitable stroke work relationship during the working phase 30, 60, and 90 minutes after cross-clamp removal showing significantly better overall left ventricular function with aerobic warm protection. (CB = cold blood cardioplegia; CC = cold crystalloid cardioplegia; WB = warm blood cardioplegia.)

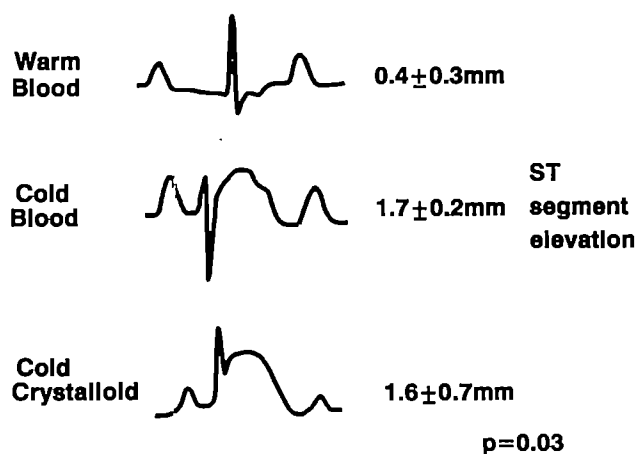


Fig 7. Electrocardiograms from a representative animal in each group comparing ST segment changes. Electrocardiographic signs of injury are significantly less in the warm blood cardioplegia group. Data are shown as the mean $\pm$ the standard error of the mean.

electromechanical arrest and hypothermia to minimize the resultant deleterious effects on cellular metabolism, energy stores, and structure [8].

Potential limitations of cold ischemic protection are well recognized and include patients with acute injury, diminished functional reserve, and prolonged operation. A novel myocardial protection technique using continuously delivered oxygenated normothermic blood cardioplegia [1] has the potential to improve myocardial protection in these difficult subsets of patients. This warm cardioplegic technique theoretically avoids an ischemic period. The principle of cardiac operation in a motionless field is achieved with hyperkalemic electromechanical arrest. This diastolic arrest in turn reduces the myocardial energy requirements to low levels [9, 10]. These lowered energy requirements appear to be met by a continuous

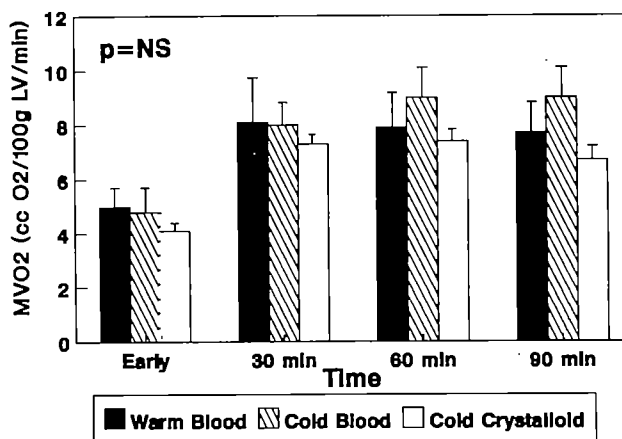


Fig 8. Comparison of myocardial oxygen consumption (MVO₂) between groups 10 minutes (early), 30 minutes, 60 minutes, and 90 minutes after cross-clamp removal. There were no significant differences (NS) between groups. Data are normalized per 100 g of left ventricle (LV).

but reduced supply of oxygen and substrate from aerobic blood cardioplegia through standard antegrade or retrograde delivery systems [11]. Those enzyme-mediated cellular homeostatic mechanisms impaired by hypothermic techniques but unaffected by hyperkalemic arrest can proceed by virtue of the normothermic state [12].

Warm heart surgery was introduced clinically by Lichtenstein and colleagues [1, 2] at the University of Toronto. A consecutive series of 121 patients undergoing coronary revascularization received warm blood cardioplegia and were compared with a historical cohort of 133 patients protected with standard hypothermic techniques [2]. The patients in the aerobic warm surgical group fared significantly better judged by a number of important clinical end points. They had fewer myocardial infarctions, a decreased incidence of low cardiac output syndrome, and less need for balloon counterpulsation. More than 99% of this group returned to sinus rhythm spontaneously after cross-clamp removal compared with about 1 of every 10 patients receiving cold ischemic protection.

The Toronto surgeons [3] then reported the expanded use of the aerobic warm myocardial protection regimen to a higher-risk group including elderly patients and patients requiring emergent operation, encompassing valve operations as well as coronary revascularization. Again, the new cardioplegic technique worked well: only 3% died, 7% required intraaortic balloon pump use, and 6% had a perioperative myocardial infarct in this high-risk population.

Yau and co-workers [13] subsequently compared different flow rates and hemoglobin concentrations for continuous warm blood cardioplegia in patients and found significantly increased MVO_2 during cardioplegia and increased myocardial adenosine triphosphate levels after cross-clamp removal in the high-flow, high-hemoglobin warm group compared with other warm and cold groups. Compliance was also better in the high-flow, high-hemoglobin group, but no significant difference was found in overall or systolic ventricular performance. Notably, only antegrade delivery was used, and the warm blood cardioplegia was interrupted while the distal anastomoses were placed. These warm ischemic periods were compensated by replenishing antegrade aortic and vein graft infusions.

The early clinical trials are encouraging and do not appear to have demonstrated any major negative functional effects of the retrograde aerobic warm technique. Because improvement in the care of patients with difficult myocardial protection problems would be a real clinical advance, further investigation in this setting is worthwhile.

For the current study, a canine model was used that allowed sophisticated analyses of left ventricular myocardial protection not readily obtainable in patients. The new aerobic warm technique was compared with two commonly used cold ischemic techniques to maintain clinical relevance. Differences in timing of doses, continuity and route of delivery, temperature, and composition of solutions in this study were all done with the intent of optimizing the currently practiced clinical methodology

for each technique. For example, retrograde delivery of some cold crystalloid cardioplegia was included to minimize distribution problems, the cold blood technique included a warm/modified/enriched reperfusate, and the warm cardioplegia was given continuously throughout the cross-clamp period. Continuous retrograde maintenance delivery of cold cardioplegia was not done and could have unfairly favored the warm group, as continuous hypothermic cardioplegia may be detrimental to functional recovery [2].

In this model of acute global myocardial ischemia, two critical end points that readily translate into clinical relevance clearly favored warm blood cardioplegia over hypothermic ischemic methods. Both myocardial mechanical performance and electrocardiographic assessment of injury were significantly better in the warm protection group.

Systolic function was assessed by the time-varying elastance model. Quantification and comparison are based on the slope of this linear relationship, $E_{\max}$. This methodology has been extensively studied and validated as a correlate of myocardial contractility or systolic function over the range of physiologic preload and afterload [5]. All groups had satisfactory recovery of contractility. Although the differences were not significant, contractility in the WB group exceeded that in the CB animals, which in turn surpassed the CC group values. These relationships persisted over time.

Although ventricular diastolic properties are notoriously difficult to assess, diastolic function significantly affects overall myocardial performance [6, 8]. Stress-strain measurements allow comparison of compliance while minimizing parallel viscous properties [6]. Nevertheless, the true stress-strain correlation or measure of intrinsic stiffness remains elusive. Numerous equations have been put forth to describe the diastolic pressure-volume relationship [14, 15]. Glantz [15] extensively reviewed the general problems associated with any of the proposed isolated indices of ventricular stiffness. Less problematic is the empiric comparison of data to determine whether or not measured diastolic pressure-volume curves are shifted or different. The task then becomes a linear regression problem [15]. Individual calculated stress-strain values for all animals at each time were pooled into the three groups and linear regression analyses carried out. The cold groups had significantly higher slopes corresponding to a decreased compliance compared with the WB group. This demonstrates a requirement for higher filling pressures to achieve a given preload volume in the cold protection groups. Speculation as to the mechanism of the poor compliance in the cold groups is outside the scope of this study; however, greater myocardial edema is not suggested by the water content study, which was the same for all three groups.

Overall ventricular function was assessed by the PRSW relationship as described by Glower and associates [7]. The relationship correlates cardiac performance as measured by stroke work to end-diastolic volume under changing preload conditions and is dependent on both systolic and diastolic properties. Data from this study

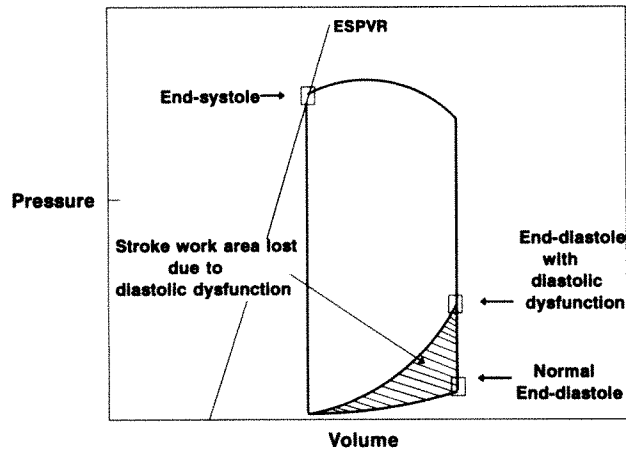


Fig 9. Pressure-volume relationship, illustrating potential for the detrimental effect of impaired diastolic function on pressure-volume area. (ESPVR = end-systolic pressure-volume relationship.)

demonstrate significantly better global ventricular function in the WB group as measured by PRSW. Because there were no significant differences in ventricular systolic function between groups, this suggests that an important part of the observed overall effect may be due to differences in diastolic function between groups (Fig 9). The CB group was superior to the CC group in overall ventricular performance. It is interesting that the CB group had an intermediary position in functional result as well as in the time course of development or evolution of these techniques. It was the only group to show improvement over time. The superior function of the WB cohort was evident immediately after separation from CPB, yet it did not improve with time. Inferior function was evident immediately after separation from CPB in the CC group and did not improve over time.

Electrocardiographic analysis also strongly favored the WB-protected hearts. This supports similar findings from the clinical studies presented earlier. These data indicate that warm blood cardioplegia, in addition to its myocardial protective effect, may actually help resuscitate the acutely damaged heart.

The mechanism of this resuscitative effect is still hypothetical, but it is clear that even though depletion of high-energy phosphate compounds occurs at a much slower rate during anaerobic hypothermic arrest, in some cases it may continue until irreversible cell damage has occurred [16]. Clinical studies [13, 17] have shown superior preservation of high-energy phosphate levels and decreased lactate accumulation with continuous warm blood cardioplegia versus intermittent cold blood cardioplegia. This implies that warm blood, in addition to maintaining electromechanical arrest, continuously supplies oxygen and substrate to the heart and allows metabolic pathways to proceed with aerobic metabolism. However, no studies to date have shown repletion of high-energy phosphate compounds using continuous warm blood cardioplegia after ischemic injury, and this warrants further investigation.

Our finding of similar histologic evidence of cellular damage in all groups demonstrates that none of these protection methods totally reversed the damaging ischemic effects or eliminated the subsequent reperfusion insult in this model of global ischemia.

Myocardial oxygen consumption showed no difference between groups. It is not possible to tell from our data the WB group incurred less oxygen debt during the cross-clamp period as previously seen by Matsuura and associates [18]. Theoretically this debt could have resulted in a larger oxygen consumption in the CC and CB group during the early reperfusion period [13], but this was not seen. Alternatively, one could hypothesize that the MVC would be lower in the hearts more severely injured immediately after cross-clamp removal as the result of an inefficiency of oxygen extraction and utilization because of more severe cellular metabolic derangement. This requires further study to draw any definite conclusions.

There was also no difference in myocardial water content between the three groups. This demonstrates that continuous warm blood cardioplegia does not result in an increase in myocardial edema compared with the intermittent cold crystalloid or cold blood methods.

The WB group required fewer attempts at defibrillation after reperfusion as is seen clinically [1-3, 19]. This may be explained by the uniformity of myocardial temperature at the time of cross-clamp removal in the WB group compared with the CC and CB groups, where uneven rewarming can cause differential speed of depolarization which can result in fibrillation.

One recent study [20] reported exacerbation of acute regional ischemic injury with warm blood cardioplegia; however, this study used antegrade cardioplegic delivery exclusively, which may not deliver cardioplegia adequately to the areas of myocardium distal to major coronary stenoses. Retrograde delivery would appear to be a rational part of the warm blood technique, as it more assuredly delivers cardioplegic solution to all areas of the myocardium [21].

Avoiding ischemic injury during aortic cross-clamp is fundamentally dependent on supplying sufficient energy to meet myocardial metabolic demands [8, 22]. Electromechanical arrest alone has clearly been shown to reduce MVO_2 by 65% to 90% with hypothermia contributing another 5% to 25% [2, 9, 10]. However, even during profound (4°C) hypothermic arrest, the myocardium still requires a supply of energy to maintain basic cellular metabolic processes, ionic homeostasis, and cell membrane stability. There is ample evidence that anaerobic glycolysis is inadequate to meet these demands for extended periods [16, 23]. Furthermore, profound hypothermia impairs glycolysis and anaerobic energy utilization [22]. Current hypothermic ischemic techniques allow a variable degree of deterioration in heart function during the cross-clamp period. Although this deterioration occurs at a reduced rate, glucose and adenosine triphosphate utilization are decreased to a greater degree, resulting in a net negative energy balance [1, 24]. Anaerobic techniques may also make the heart vulnerable to reperfusion injury after aortic cross-clamp removal [2]. In a

attempt to overcome the problems of anaerobic cold arrest, Rosenkranz and colleagues [25] used normothermic induction of blood cardioplegia with intermittent cold maintenance doses. Furthermore, Teoh and associates [26] and Rosenkranz and co-workers [27] demonstrated accelerated myocardial metabolic recovery with terminal warm blood cardioplegia.

The obvious progression of this line of reasoning is that if warm *induction* and *terminal* warm cardioplegia are beneficial to myocardial recovery, warm *maintenance* of arrest is worthy of investigation. The warm technique theoretically avoids many of the potential problems associated with anaerobic cold arrest by allowing the heart to continue using oxygen and substrate for energy production and maintenance of normal cellular metabolism [1].

However, the warm technique presents some new technical problems. These relate primarily to the difficulty with visualization during coronary bypass procedures compared with the asanguineous field associated with hypothermic techniques. Excellent visibility is crucial for reliable, faultless coronary operations. Concern for this may dissuade surgeons from using this technique unless compelling scientific evidence suggests that the warm technique offers clear-cut patient benefit.

Both the clinical trials and the results from this study suggest that the warm blood technique is both safe and effective. These data suggest an advantage for warm blood cardioplegia in the setting of acute ischemia. The data do not yet support the use of warm blood in the majority of cases, but in this canine model, the results indicate that this technique may resuscitate and protect acutely ischemic myocardium significantly better than standard hypothermic regimens. This was demonstrated by improved recovery of global and diastolic myocardial function, less electrocardiographic injury, and prompt return to sinus rhythm after reperfusion. Continuous aerobic warm blood cardioplegia warrants further clinical and laboratory investigation to define the mechanisms of protection, as it appears to have the potential for an important role in cardiac surgery.

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Appendix 1. Derivation of Stress and Strain Data Points

The left ventricle is modeled as a thin ellipsoidal shell with three unequal orthogonal axes. Laplace's formula for thin-walled ellipsoids was used to calculate wall stress (σ), as it has previously been shown to be the most accurate [28]. The lengths of the axes were measured by three pairs of sonomicrometer crystals placed on the endocardial surface as previously described [4]. The base-apex crystal pair (BA) was used to measure the major-axis length. The septal-free wall (SFW) and anterior-posterior (AP) crystal pairs were used to measure and calculate the minor-axis length. The minor axis (A_{mj}) was calculated as the arithmetic average of the SFW and AP lengths, as Laplace's formula assumes symmetry of the minor axis:

$$A_{mj} = (SFW + AP)/2. \quad (1)$$

Because the "base" crystal was placed epicardially, a correction factor (representing the myocardial thickness at the placement of the base crystal) of 0.3 cm was subtracted from the measured length to obtain the corrected length (BA_c):

$$BA_c = BA - 0.3 \text{ cm}. \quad (2)$$

This correction was previously found to be the average thickness of myocardium measured post mortem in the area of crystal placement in previous experiments in this laboratory.

The major axis (A_{mj}) is equal to the corrected base-apex length:

$$A_{mj} = BA_c. \quad (3)$$

The ellipsoidal shell volume (V_s), used to calculate the midwall circumferential stress, was calculated by finding the volume of the ellipsoid based on the endocardial crystals (V_i) and subtracting this from the ellipsoidal volume calculated as if the crystals were placed epicardially (V_e):

$$V_s = (V_e - V_i). \quad (4)$$

The formula for the internal ellipsoid volume is:

$$V_i = \pi/6 \times (SFW)(AP)(BA_c). \quad (5)$$

The volume of V_e must be derived by adding the average mid-circumferential wall thickness (h) to each axis length. The calculated external diameters of the SFW and AP lengths are

simply the respective length plus $2 \times h$. Along the BA axis, the wall thickness has been shown to be 55% of that in the other areas by previous studies (29). Therefore $2 \times 0.55 h$ is added to the BA_c length. Thus, the external ellipsoid volume equation is:

$$V_e = \pi/6 \times (SFW + 2h)(AP + 2h)(BA_c + 1.1 h). \quad (6)$$

The mass of the left ventricle (M), measured post mortem, is equal to the shell volume (V_s) multiplied by the specific gravity of normal myocardium:

$$M = 1.07(V_s). \quad (7)$$

By substituting equation 4 into equation 7, this becomes:

$$M = 1.07(V_e - V_i). \quad (8)$$

By substituting equations 5 and 6 into equation 8, the mid-circumferential wall thickness (h) can be iteratively determined, as all other variables are known. The average thickness for all end-diastolic points is then calculated and stored as h .

Stress (σ) is calculated using the formula of Laplace. This formula calls for major-axis and minor-axis midwall radii; therefore, one wall thickness must be added to each axis length (a diameter) and the sum divided by two. This yields the equation for minor-axis midwall radius (Mi_{mwr}):

$$Mi_{mwr} = (A_{mj} + h)/2. \quad (9)$$

Likewise the major-axis midwall radius (Mj_{mwr}) is calculated from the major-axis diameter measurement, taking into consideration that the wall thickness is only 55% of the average midwall thickness for the minor axis:

$$Mj_{mwr} = (A_{mj} + 0.55h)/2. \quad (10)$$

The radii can be substituted into the ellipsoid modification of Laplace's formula for midwall circumferential stress (σ):

$$\sigma = 1 - \frac{(Mi_{mwr})^3}{(LVP \times Mi_{mwr})/h \times [(Mj_{mwr})^2 \times (2Mi_{mwr} + h)]} \quad (11)$$

where LVP is left ventricular pressure.

Lagrangian strain (ϵ) is calculated based on an unstressed left ventricular volume (V_0), which is obtained at the end of a sustained period of vena cava occlusion allowing maximum emptying of the heart and at a time when the left ventricular pressure is equal to 0 or at a minimum. Strain (ϵ) at any end-diastolic volume (V) is:

$$\epsilon = (V - V_0)/V_0. \quad (12)$$

The midwall circumferential stress (σ) and Lagrangian strain (ϵ) were calculated for each end-diastolic time point during a 6-second period of rapidly decreasing preload.

DISCUSSION

DR WILLARD M. DAGGETT (Boston, MA): Such an elegant study with beautiful physiology is what we have come to expect from your group, Dr Brown. I have a couple of comments that relate to your study as well as other studies presented in this session and that concern the basic concept of continuous warm blood cardioplegia apart from the problems that may be related to the delivery, whether antegrade or retrograde.

My colleagues and I have just completed a study in which we

measured peak creatine kinase levels after coronary bypass procedures in three groups of patients: patients with intermittent oxygenated dilute cold blood cardioplegia, patients with continuous warm blood cardioplegia delivered antegrade, and patients with continuous warm blood cardioplegia delivered retrograde. The lowest values, and they were strikingly low, were in the group with antegrade delivery of continuous warm blood cardioplegia. The second best levels were achieved with intermittent

oxygenated dilute cold blood cardioplegia, and the worst values were with continuous retrograde delivery. We heard earlier today about the persistence of electrical and associated mechanical activity with continuous warm blood cardioplegia. I do not think that is a problem when we are delivering blood cardioplegia antegrade at arterial pressure through the grafts. It may present serious problems of distribution when delivery is retrograde through veins at low pressure.

DR BROWN: My only comment is that other investigators have shown that antegrade continuous warm blood cardioplegia in the presence of critical coronary stenoses appears to be associated with suboptimal protection. This is perhaps in part due to maldistribution to those areas of myocardium distal to the area of blockage, whereas retrograde cardioplegia appears to distribute better to these areas.

DR IRVIN B. KRUKENKAMP (Boston, MA): I also congratulate you on a fine study. I can reinforce your findings with some data my colleagues and I have recently accumulated using the pig heart in a similar model of acute occlusion of the left anterior descending coronary artery (LAD) followed by retrograde warm or cold cardioplegia. In the cold group, there was a functional deficit both globally and regionally of approximately 29% compared with 100% recovery of function in the warm group.

Measuring myocardial oxygen consumption during the cross-clamp period in our model, we obtained a control oxygen utilization of 0.85 mL per 100 g of left ventricle per minute that increased on removal of the LAD snare to 1.2 and then fell to 1 mL · 100 g⁻¹ · min⁻¹ at the end of the ischemic period before reperfusion. We consider this an oxygen utilization for repair.

Do you have any data on regional oxygen consumption or regional cardiac mechanics, as your model is really one of regional stunning and ischemia? To follow-up on Dr Daggett's comment regarding the delivery of cardioplegia by the retrograde route, there are obvious differences between dog hearts, pig hearts, and human hearts. Do you have any data in that regard?

DR BROWN: I do not have any specific data regarding comparative delivery of retrograde cardioplegia in porcine versus canine versus human hearts. Individual studies of retrograde flow and coronary venous anatomy exist for each of these species, however. We did do some regional functional studies using the regional analogue of preload recruitable stroke work. There was a fair amount of variation in the numbers, and we were not able to discern a difference either regionally within an animal or across the three groups in terms of regional stroke work because of this variability.

DR RICHARD M. ENGELMAN (Springfield, MA): In the animal study that you did, did you discover any change between warm and cold in the incidence of intraventricular conduction disturbances? You mentioned T wave abnormalities after reperfusion. I wonder if the animals behaved as humans do, which, in our hands at least, means there is an incidence of cold-induced conduction disturbance. We do not see this with the effects of reperfusion during warm protection.

DR BROWN: In our electrocardiographic analysis, we did see prolongation of the QRS complexes but did not quantitate that; however, no animal required pacing for separation from cardiopulmonary bypass.

Total Anomalous Pulmonary Venous Connection in Neonates and Young Infants: Repair in the Current Era

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Total anomalous pulmonary venous connection has been one of the more challenging congenital heart defects in newborns and young infants despite improvements in surgical technique, cardiac anesthesia, neonatal myocardial preservation, and postoperative care. Since 1981, 30 patients with total anomalous pulmonary venous connection have undergone primary total correction. Mean age at operation was 28 ± 6 days and mean weight, 3.3 ± 0.7 kg. Essential features of the surgical approach in these small patients included early surgical intervention, profound hypothermia with total circulatory arrest, cardioplegic myocardial preservation, and a wide posterior anastomosis. Operative mortality was $13\% \pm 6\%$. All four deaths were in patients having emergency operation within 24 hours of the surgical consult and requiring

ventilator support preoperatively. The mean follow-up is 47 ± 7 months. There have been two late deaths, and the 7-year survival rate is $79\% \pm 8\%$. There have been two reoperations, and $91\% \pm 6\%$ of the patients are reoperation free at 7 years. Only 1 of the 24 surviving patients is symptomatic. Growth in survivors is closely monitored. The height growth percentile is less than 5% in $15\% \pm 8\%$ of survivors and the weight growth percentile, less than 5% in $17 \pm 8\%$. During the past decade, with a consistent surgical approach to neonates and infants with total anomalous pulmonary venous connection, it has been possible to achieve low early mortality, low attrition, and excellent late results.

(*Ann Thorac Surg* 1993;55:43-9)

Total anomalous pulmonary venous connection (TAPVC) is a rare congenital cardiac anomaly, seen in only 1% of patients with congenital heart disease. It is a life-threatening anomaly when present, and few patients live beyond the first year of life without surgical correction. Over the last decade, substantial improvements have been achieved in surgical technique, cardiac anesthesia, myocardial preservation, and postoperative care of patients with this disease. Despite this progress, TAPVC in neonates and young infants continues to challenge the abilities of pediatric cardiac services. Over the last 10 years at the Oregon Health Sciences University, a consistent approach to repair with early surgical intervention has been followed. The purpose of this report is to review and illustrate current results with repair of TAPVC in a regional pediatric cardiac surgery center.

Patients and Methods

Patient Selection

All patients with TAPVC referred to the University Hospital between July 1981 and July 1991 form the basis of this review. The clinical characteristics of these patients are summarized in Table 1. The mean birth weight of the patients was 3.2 ± 0.1 kg; the distribution is shown in

Figure 1. The mean age at operation was 28 ± 6 days (range, 12 hours to 15 months), and the mean weight was 3.3 ± 0.7 kg (Figs 2, 3). The infradiaphragmatic type of TAPVC was the most frequent and was seen in 17 patients (56.7%). The supracardiac type was present in 8 patients (26.7%) and the intracardiac type, in 5 (16.7%).

The mean pulmonary artery systolic pressure was 75.4 ± 2.0 mm Hg (range, 45 to 125 mm Hg) before operation in the patients who had cardiac catheterization. The most common associated cardiac anomaly was a patent foramen ovale, which kept these patients alive. Five patients had a patent ductus arteriosus that was closed at the time of cardiac repair. Two patients had pinhole ventricular septal defects.

During the earlier years, it was routine to perform cardiac catheterization soon after arrival of the patient at the neonatal intensive care unit to diagnose and delineate the exact type of problem. In later years, almost all diagnoses were made by echocardiography alone (7 patients). Fifteen patients (50%) were diagnosed as having pulmonary venous obstruction by a combination of chest roentgenograms and cardiac catheterization.

Once the diagnosis was established, all patients had early repair. In 19 patients it was possible to wait for the next scheduled operating slot, usually within 24 to 36 hours of diagnosis (urgent cases). Eleven patients had emergency procedures within 24 hours after brief periods of stabilization. Most of the earlier patients had balloon atrial septostomy, and those with intractable tachypnea

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Table 1. Summary of Clinical Characteristics

Variable	No. of Patients ^a
Mean age (d)	28 ± 6
Type	
Supracardiac	8
Intracardiac	5
Infradiaphragmatic	17
Cyanosis	27
Tachypnea	23
Tachycardia	21
NYHA class III	6
NYHA class IV	24
Pulmonary venous obstruction	15
Intubation	13
Inotropic support	9

^a Data are shown as number of patients except for mean age.

NYHA = New York Heart Association.

and cyanosis or congestive heart failure were sedated and treated on the ventilator.

Surgical Technique

All patients were anesthetized by a member of the cardiac anesthesia team. For the first 20 patients, the perfusion technique entailed surface cooling to 32°C followed by profound hypothermia and total circulatory arrest and subsequent rewarming on bypass. In the last few years, surface cooling has been abandoned, and slow cooling to 17° to 18°C on bypass and a period of arrest have been used. Myocardial protection was achieved by potassium-induced cold cardioplegia with injection of 200 to 300 mL of the solution at 4° to 5°C into the aortic root right at the start of circulatory arrest.

In patients with supracardiac or infradiaphragmatic connection, the heart was lifted cephalad and to the right to facilitate posterior mediastinal dissection over the pulmonary venous trunk. Long transverse incisions were made on this common pulmonary vein and on the left

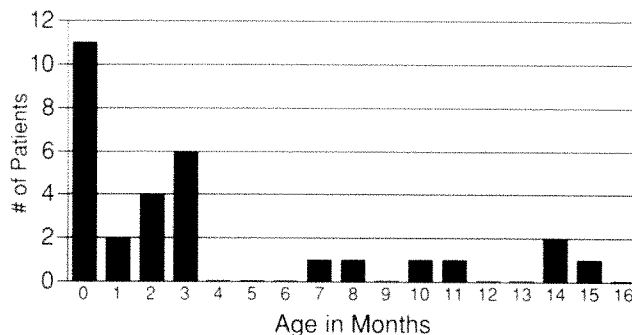


Fig 2. Age at operation for total anomalous pulmonary venous connection.

atrium (Fig 4). A wide, unrestrictive anastomosis (usually greater than 2.5 cm in length) was constructed with a running suture of 6-0 or 7-0 polypropylene (Fig 5). The vertical vein was ligated and the atrial septal defect closed in all patients.

In patients with intracardiac connection, all of whom had return to the coronary sinus, the approach was through a longitudinal right atriotomy. The septum between the enlarged coronary sinus and left atrium was everted into the patent foramen ovale and widely excised (Fig 6). The foramen ovale was closed primarily in most patients; occasionally a small patch was necessary. All coronary sinus blood was diverted to the left atrium by patch closure of the coronary sinus ostium (Fig 7). Particular attention was given to insert the patch within the ostium and away from the conduction tissue, particularly around its anterior perimeter.

Data Analysis

Data analysis was performed by the Office of Research Development and Utilization, Oregon Health Sciences University. Mean values were calculated for continuous, interval-level variables. All means were reported with standard errors (mean ± 1 standard error). Inferential analysis was performed using Fisher's exact test. This test is appropriate for comparisons of two samples with di-

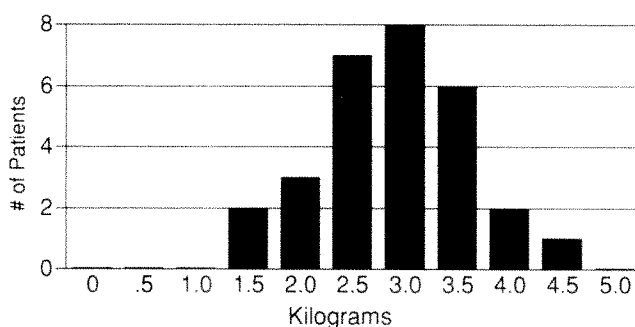


Fig 1. Birth weight distribution of patients undergoing surgical repair of total anomalous pulmonary venous connection.

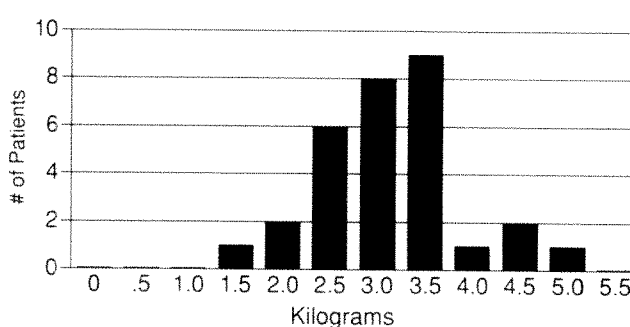


Fig 3. Weight distribution of patients at operation for total anomalous pulmonary venous connection.

chotomous outcomes when sample sizes are small. Analysis of time-related events was performed using actuarial methods. Estimates were computed at 30-day intervals.

All patients who survived have been contacted or seen in the outpatient clinic within 2 months of the conclusion of this study (July 1991).

Results

The operative mortality rate was $13\% \pm 6\%$. All four deaths were associated with a low cardiac output state in patients having emergency operation and requiring intubation and ventilator support preoperatively (Figs 8, 9).

Table 2 summarizes the effect of preoperative variables on operative outcome. Presence of pulmonary venous obstruction did not affect mortality and actually was last on the list of variables examined. Important intraoperative variables included cardiopulmonary bypass time of 36 ± 10 minutes and total circulatory arrest time of 45 ± 12 minutes.

Twenty-three patients had some inotropic support postoperatively, although most received only a routine infusion of $5 \text{ g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ of dopamine hydrochloride for 24 to 36 hours. Eleven patients needed temporary pacing, mostly for the first 4 to 12 hours in the intensive care unit and principally for junctional rhythm. Twenty-four patients were extubated within 72 hours after operation. Two patients needed 92 hours and 116 hours of ventilatory support before extubation. All patients but these last 2 were feeding by mouth within 24 hours after

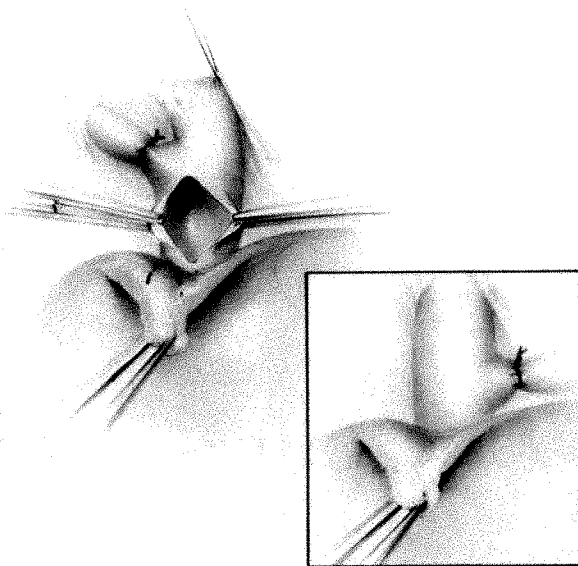


Fig 4. Surgical technique: incisions on common pulmonary venous trunk and the base of the left atrial appendage. Note ligature on vertical vein. Inset demonstrates infradiaphragmatic type.

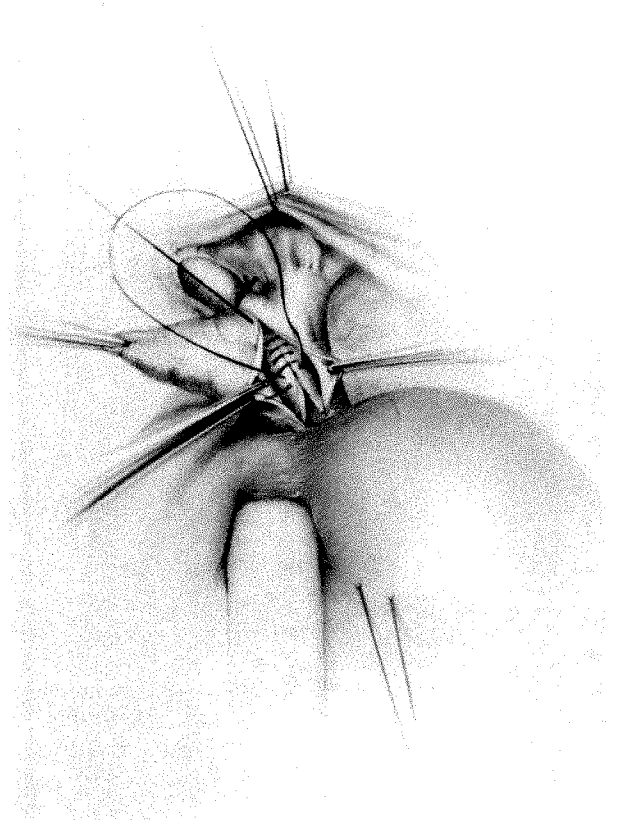


Fig 5. Long, unobstructed anastomosis between pulmonary venous trunk and left atrium.

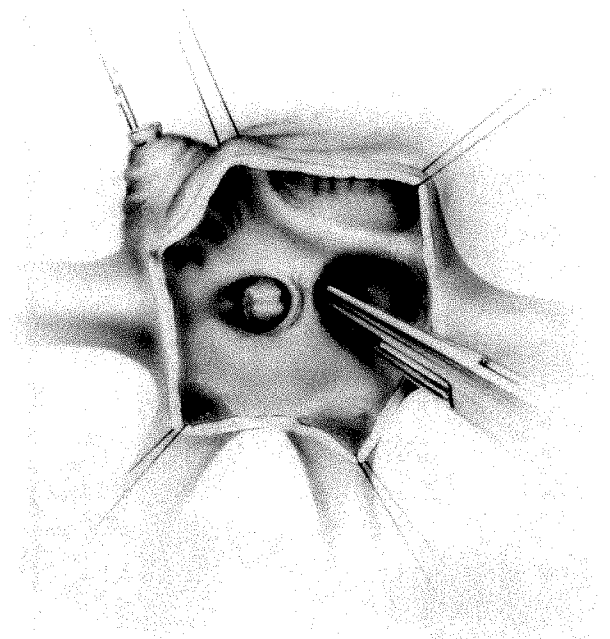


Fig 6. Surgical technique in total anomalous pulmonary venous connection of intracardiac type: The septum between the coronary sinus and the left atrium is excised.

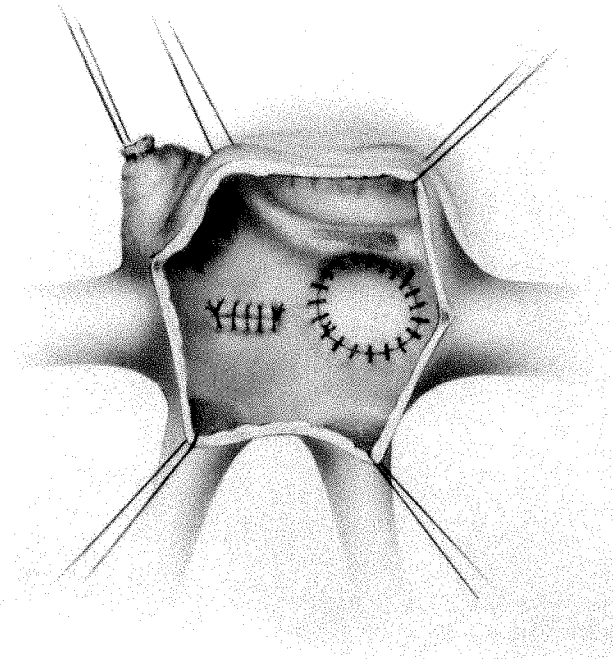


Fig 7. Primary closure of patent foramen ovale and patch closure of coronary sinus, leaving coronary sinus return into the left atrium. Note location of atrioventricular node between the patch and the tricuspid valve.

extubation. One patient had renal failure with spontaneous resolution.

Three-fourths of the patients were discharged from the hospital within 2 weeks after operation. The other 25% stayed up to 30 days. The mean follow-up is 47 ± 7 months (range, 4 to 126 months). There have been two late deaths; 1 patient died of persistent pulmonary hypertension, and the second had recurrent pulmonary venous obstruction. Actuarial survival at 7 years is $79\% \pm 8\%$ (Fig 10).

Ninety-one percent $\pm 6\%$ of the patients are free from reoperation (Fig 11). Two reoperations were performed at 3 months and 3 years, both for diffuse pulmonary venous obstruction proximal to the anastomosis. Twenty-three of the 24 patients alive are totally asymptomatic. Growth

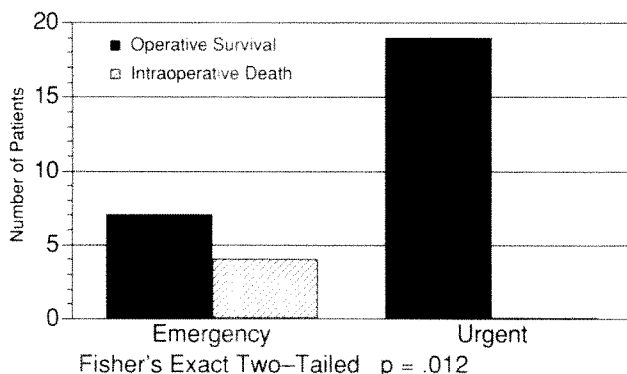


Fig 8. Emergency operation and operative mortality.

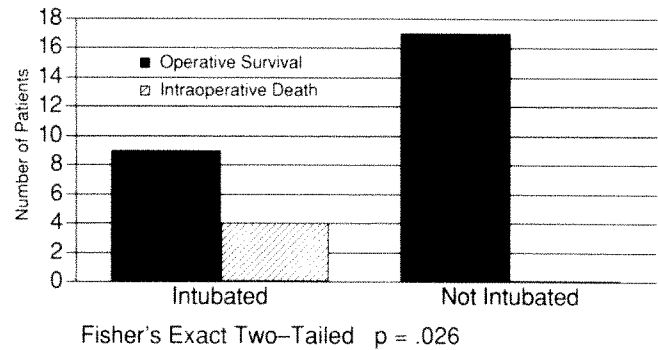


Fig 9. Preoperative intubation and operative mortality.

percentiles for height and weight have been good and are summarized in Tables 3 and 4.

Comment

It is now nearly 200 years since the first description of TAPVC [1] and 40 years since the first surgical treatment [2]. This anomaly is truly a surgical disease, and medical therapy is merely supportive and preparatory to surgical correction. Because long-term medical management would be very unusual, over the last 10 years, we have taken an aggressive approach to neonates with this disease by planning early surgical intervention after a brief period of stabilization. In our experience, older patients who are seen late in life have been very rare, and our patients mostly have been neonates and a few infants up to 15 months of age. Almost all patients were seen with cyanosis, tachypnea, and tachycardia soon after birth and quite frequently required inotropic and ventilator support before operation.

Over recent years, several groups [3-6] have reported improved results with operative intervention, and the 13% operative mortality rate in the current series compares very favorably with the rates in these reports. Of note is the large number of patients in our group who would be considered in extremis before surgical intervention. All deaths in these series occurred in patients who required emergency operation and intubation in the emergency room or neonatal intensive care unit, and all deaths

Table 2. Preoperative Variables and Operative Mortality

Risk Factor	p Value ^a
Emergency operation	0.012
Intubation preoperatively	0.026
Inotropic support preoperatively	0.069
Weight at operation < 3.0 kg	0.069
Age at operation < 1 week	0.095
Birth weight < 3.0 kg	0.178
NYHA class IV	0.387
Pulmonary venous obstruction	0.647

^a Data are based on Fisher's exact one-tailed test.

NYHA = New York Heart Association.

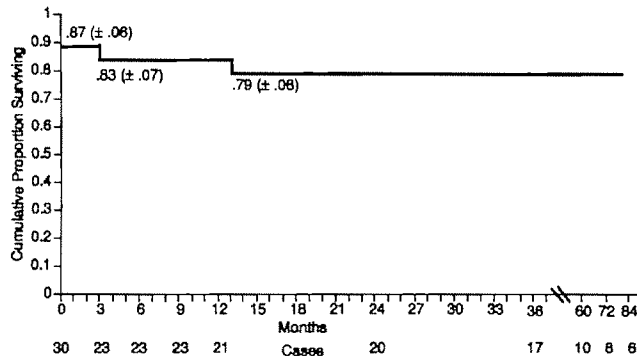


Fig 10. Actuarial survival after repair of total anomalous pulmonary venous connection.

were due to persistent low cardiac output. In a series from Vanderbilt University [7], four of the five deaths also were in patients who needed preoperative ventilator support.

This experience does not show a higher risk in relation to certain types of anomalous venous connection, particularly infradiaphragmatic type, as reported by Turley and co-workers [8] and Lincoln and associates [9]. It also concurs with the series reported by Katz and co-authors [10], which showed that anatomic type is not a determinant of surgical results.

Again, presence of pulmonary venous obstruction preoperatively did not increase surgical mortality in this series. This is in contrast to the reported higher mortality in patients with obstruction in the series by Hammon and associates [7]. Though the 15 patients with obstruction in our series were sicker, once the obstruction was relieved, recovery was fairly quick, and ventilator support beyond 72 hours was very rarely necessary. The important principles of treatment in this series were to intervene early, before substantial depletion and deterioration, and to construct an unrestrictive, wide connection between the veins and the left atrium. These measures enabled prompt resolution of the pulmonary venous obstruction and hypertension. The 72-hour ventilator support has been routine on our service and gave the relatively small and noncompliant left heart chamber time to adapt and maintain full forward cardiac output.

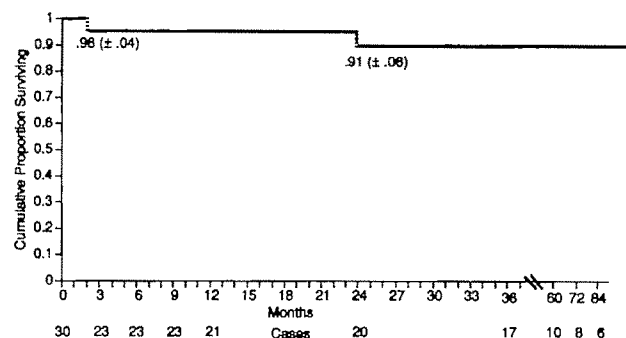


Fig 11. Proportion of patients free from reoperation after repair of total anomalous pulmonary venous connection.

Table 3. Height Growth Percentile

Percentile Growth	Frequency	%
<5	3	15
5-25	7	35
26-50	3	15
51-75	3	15
76-95	4	20
>95	0	...
Total	20	100

Total anomalous pulmonary venous connection is most often an isolated lesion, and once the operative phase is over, these patients can be expected to do well. Results are uniformly excellent in older patients who are seen late without pulmonary hypertension, but these patients are rare.

The majority of patients in our series were neonates and young infants; 78% had pulmonary hypertension, and 50% had some degree of pulmonary venous obstruction. Still, the late outcome in this group was excellent, and the attrition rate was low. Of the two late deaths, one was due to persistent pulmonary hypertension with no evidence of anastomotic or anatomical obstruction to venous return. This type of inexplicable severe pulmonary hypertension in TAPVC has been well documented [11]. In DeLisle and associates' [11] autopsy series of 93 patients with TAPVC, among patients with markedly elevated pulmonary artery pressure, one fourth had no evidence of obstruction.

The second late death was in a patient who needed two reoperations because of recurrent pulmonary venous obstruction. The stenosis was diffuse and proximal to the anastomosis and resembled a fibrosing mediastinitis with severe fibroplasia. The reoperations during the follow-up in this series involved this patient who did not survive and a second patient with similar obstruction who survived reoperation. This type of diffuse fibrosis, unremitting thickening, and hypertrophy of the endocardium at the pulmonary vein entry sites have been reported by others [3, 4, 8, 12]. The problem in our patient was clearly not anastomotic stenosis as seen by Schäfers and co-

Table 4. Weight Growth Percentile

Percentile Growth	Frequency	%
<5	4	17
5-25	10	42
26-50	4	17
51-75	2	8
76-95	3	13
>95	1	4
Total	24	101*

* 101% due to rounding.

workers [13] in their series. For this reason, we have continued to use very fine nonabsorbable monofilament suture material in the construction of the anastomosis.

The cardiac function in these patients has been uniformly excellent. All but 1 of the surviving patients are totally asymptomatic with no physical restriction. Follow-up echocardiograms of all long-term survivors have shown normal left ventricular wall motion and normal pulmonary venous flow profiles. All patients are in regular sinus rhythm. Similar late functional results have been reported by others [14-16].

These patients have had very acceptable growth and development during long-term follow-up. Height and weight growth percentiles have been less than 5% in only a small portion of the patients. Intellectual development subjectively assessed by pediatricians has been normal in all.

During the past decade, with a consistent surgical approach to neonates and infants with TAPVC, it has been possible to achieve low operative mortality. Early diagnosis and early surgical intervention without attempts at prolonged medical management are important principles of treatment. A wide, unobstructed communication between the left atrium and the common pulmonary venous trunk will provide prompt relief of the pulmonary artery hypertension and pulmonary venous obstruction. Mortality remains high when operations are done within the first 24 hours without a preparatory period to stabilize these sick neonates both metabolically and hemodynamically.

Late survival and functional states have been excellent. Diffuse fibroplasia involving pulmonary vein entry sites remains the major cause of late morbidity and mortality.

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DISCUSSION

DR KEVIN TURLEY (San Francisco, CA): I congratulate Dr Cobanoglu on his excellent results in this very difficult group of patients.

Our experience with total anomalous pulmonary venous connection dates back 17 years, and 13 years ago we reported our initial series of 22 patients with this condition operated on between 1975 and 1979. In that series, we advocated a number of changes in approach to these infants. We demonstrated age was not the determinant of survival. In fact, early operation in that series resulted in better results than in many of the previous series where attempts to palliate to prolong the preoperative period and improve the patient's condition resulted in a higher mortality. Since that initial experience, an additional 95 patients have had repair. Of this total of 117 patients, 65 (56%) underwent repair in the first month of life.

In our first series, obstruction was thought to be an important determinant of increased mortality. Fourteen of those 22 patients and all patients with infradiaphragmatic connection had obstruction. In the subsequent 95 patients, we have seen a marked reduction in the number of patients with obstruction at presentation (approximately 50%), with 80% of the patients with infradiaphragmatic type showing obstruction. The mortality rate in the original series was 13%, as in the series of Dr Cobanoglu, and in the subsequent 95 patients, it decreased to 8%. The overall mortality rate for the 117 patients was 9%. In our series as in the series just presented, obstruction is not a determinant of survival.

Finally, in our original 22 patients, the type of lesion was thought to be of importance. Two of our 6 patients with infradiaphragmatic connection died early, and 2 additional patients died late. Those 6 patients represented only 27% of that series,

whereas in the series of Dr Cobanoglu, 57% had infradiaphragmatic connection.

Although the mortality rate has decreased from 13% to 8% in our series, a higher mortality continues to be seen in patients with infradiaphragmatic connection, and it is in this group where the late mortality resulting from diffuse pulmonary venous obstruction occurs. Thus, although type, as Dr Cobanoglu noted, is not a determinant in itself, patients with infradiaphragmatic or mixed-type connection have a higher incidence of small, thick-walled pulmonary veins as opposed to the thin-walled, dilated, proximally obstructed pattern most commonly seen.

In our series, 2 patients with infradiaphragmatic type had persistent pulmonary hypertension. I think this is associated with total anomalous pulmonary venous connection and is a condition we currently cannot treat. However, 6 of the patients had diminutive pulmonary veins. Dr Cobanoglu, did you note the size and configuration of the veins in the patients in your series and in those who have had problems, specifically those with the infradiaphragmatic lesion?

One of your patients is currently symptomatic. Would you describe this patient in more detail as well as the type of lesions in the 4 patients who died early and the 2 who died late?

DR COBANOGU: Thank you very much, Dr Turley. I will echo some of your remarks. We approach these patients very aggressively when they arrive at the neonatal intensive care unit and do not spend days attempting to stabilize their condition metabolically or hemodynamically. We usually try to do whatever we can within a few hours, or within the first 24 hours certainly, and then schedule them for operation. I think some of the improvement is due to this early intervention.

At operation, the surgeon clearly becomes concerned at times after looking at the posterior mediastinum and doing the dissection to delineate the pulmonary venous tract and the veins. I agree with you completely that I feel uneasy about the long-term outcome, not necessarily about the immediate outcome, when I see somewhat thick and small veins entering a large common tract. I know that we can achieve a wide anastomosis in the common tract area, but when the veins entering the collecting vein are thick and somewhat small, this is very bothersome.

As for the patients who died, we did not see a preponderance of a particular anatomic type. In our experience, anatomic type did not correlate with mortality. Among the patients who died, 1 had intracardiac connection, 1 had supracardiac connection, and 2 had infradiaphragmatic connection. Preoperative pulmonary

venous obstruction was seen mostly in patients with infradiaphragmatic connection. As reported in the literature, intracardiac connection in itself is no longer considered a risk factor, and our experience supports this.

DR STEVEN R. GUNDRY (Loma Linda, CA): I congratulate on their very fine results and will briefly present our results, which were recently presented by our fellow, Javier Alonso de Begona, at the Asian cardiothoracic meeting.

My colleagues and I have operated on 33 patients since 1978 and have found much of what the Portland group found. In our series there has been only one death, an infant who was brought to the operating room under full cardiopulmonary resuscitation with ventricular fibrillation. Although he was in stable condition postoperatively, he died of multiorgan failure days later. There have been no late deaths and only one reoperation for pulmonary venous stenosis of a single pulmonary vein. We could find no correlation between survival or late follow-up and type of lesion.

We echo your sentiments that in this day and age, this is no longer a dangerous lesion. We think that the use of circulatory arrest and the variety of surgical approaches have influenced the results. Examples of approach include the transatrial approach, used by my colleague Dr Leonard Bailey, and the superior lifting of the heart approach, which I tend to favor. Both work equally well.

To repeat, I think the expeditious approach to this lesion has totally changed its management.

DR JOSEPH J. AMATO (New Hyde Park, NY): I also congratulate Dr Cobanoglu on his excellent presentation about this complex anomaly. As you had a preponderance of intracardiac type, I wonder whether you ligate and divide the distal pulmonary vein. It was observed in Mr Stark and Dr de Leval's book *Surgery for Congenital Heart Defects* that necrosis of the liver may occur after ligation. I have always divided the distal vein and have never encountered this. Did such necrosis occur in your series, or can you add any knowledge to this topic?

DR COBANOGU: Hepatic necrosis has not been a problem in my experience. The vertical vein, regardless of its direction (infradiaphragmatic or toward the innominate venous system), was closed at the end of the procedure in every patient. We have been very careful about not closing it early during the operation and have used it to vent the left side of the heart during rewarming and resuscitation.

Effects of University of Wisconsin Solution on Endothelium-Dependent Coronary Artery Relaxation in the Rat

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University of Wisconsin (UW) solution has been reported to enhance myocardial preservation in heart transplantation. To evaluate the effects of UW solution on coronary artery endothelial function, we designed experiments to compare UW solution with a standard crystalloid hyperkalemic cardioplegic solution (CHCS). Isolated rat hearts were studied in a modified Langendorff apparatus for coronary endothelial function. Groups 1 and 2 were perfused with 4°C CHCS (24 mmol/L of KCl) and UW solution, respectively, for 10 minutes at a pressure of 80 cm H₂O, whereas group 3 underwent warm ischemia for 10 minutes. Groups 4 and 5 were perfused with and stored for 4 hours in cold (4°C) CHCS and UW solution, respectively. Group 6 underwent 4 hours of topical cooling (4°C) without any cardioplegic perfusion. All groups had 6 hearts each. Endothelium-dependent relaxation and endothelium-independent relaxation of the coronary arteries were tested by infusing 5-hydroxytryptamine (5HT) (10^{-6} mol/L) and sodium nitroprusside (10^{-5} mol/L), respectively, before and after perfusion with and storage

in one of the two cardioplegic solutions. The coronary vasodilatation induced by 5HT and sodium nitroprusside was not altered in hearts perfused with (group 1) or perfused with and stored in CHCS (group 4). Coronary flow increase after 5HT infusion was significantly decreased in hearts perfused with (group 2) (before, $35\% \pm 10\%$; after, $13\% \pm 10\%$; $p < 0.01$) or perfused with and stored in UW solution (group 5) (before, $34\% \pm 5\%$; after, $-5\% \pm 12\%$), indicating severe endothelial dysfunction. In the latter group, coronary flow increase with sodium nitroprusside was also decreased, a finding suggesting smooth muscle damage (before, $84\% \pm 35\%$; after, $30\% \pm 15\%$). Coronary arteries of hearts having 4 hours of cold ischemia alone (group 6) had a significant decrease only in flow response to 5HT stimulation (before, $60\% \pm 23\%$; after, $24\% \pm 12\%$). These experiments suggest that perfusion with and storage in UW solution does not preserve endothelium-dependent coronary relaxation in the isolated rat heart.

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Optimal myocardial preservation remains a major concern in heart transplantation. Acceptable myocardial protection can be obtained for 4 to 6 hours with a cardioplegic or normal saline rinse followed by cold crystalloid preservation [1, 2]. Encouraging results have been obtained both experimentally and clinically in heart transplantation with the use of University of Wisconsin (UW) solution. However, the usefulness of this solution in enhancing long-term heart preservation is still controversial [3-8]. First designed for preservation of the pancreas, and then kidney and liver preservation, its application to heart transplantation has raised hope for a longer period of optimal preservation. Despite the fact that UW solution could contribute to the improvement of myocardial preservation during storage, the effect on coronary artery endothelial reactivity has not been determined.

The vascular endothelium plays a major role in arterial vasoregulation. Besides producing antithrombotic substances such as prostacyclin, antithrombin III, plasmin

activator, protein C, and α_2 -macroglobulin, endothelial cells release nonprostanoid vasoactive compounds called endothelium-derived relaxing factors (EDRFs), nitric oxide being one of these [9-12]. Release of nitric oxide has major effects on local vasoregulation, not only because nitric oxide is a powerful muscle relaxant, but also because it is an inhibitor of platelet adhesion and aggregation. Loss of endothelial responsiveness during myocardial storage will increase the thrombogenicity of the vascular wall to the aggregating platelets and could compromise the blood supply of the donor heart. It also has been reported that vessels with chronically regenerated endothelium do not resume normal vasoregulatory function but rather have an increased risk of vasospasm [13-16]. Then it is imperative to preserve the vascular endothelial function of the donor heart to assume optimal graft survival.

Previous reports indicate that infusion of crystalloid hyperkalemic cardioplegic solution (CHCS) could impair 5-hydroxytryptamine (5HT)-induced endothelium-dependent coronary relaxation in the isolated Langendorff-perfused rat heart, although others have claimed that this impairment might be related to mechanical and time

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Table 1. Composition of Crystalloid Hyperkalemic Cardioplegic Solution and University of Wisconsin Solution

Component	Amount
Crystalloid Hyperkalemic Cardioplegic Solution	
Na ⁺ (mmol/L)	130
Cl ⁺ (mmol/L)	135
Ca ²⁺ (mmol/L)	3
Lactate (mmol/L)	28
Mannitol (g/L)	20
NaHCO ₃ (g/L)	0.17
KCl (mmol/L)	24
pH	7.25
University of Wisconsin Solution	
KH ₂ PO ₄ (mmol/L)	25
MgSO ₄ (mmol/L)	5
Adenosine (mmol/L)	5
Glutathione (mmol/L)	3
Raffinose (mmol/L)	30
Allopurinol (mmol/L)	1
Potassium lactobionate (mmol/L)	100
Pentastarch (g/L)	50
Insulin (IU)	40
pH	7.27

factors rather than CHCS infusion itself [17-19]. No data, however, are available on the effect of UW solution perfusion and storage on the coronary vasoregulation of the rat heart.

This study was designed to evaluate the effect of UW solution on endothelium-dependent coronary artery relaxation in the isolated rat heart model after perfusion with and cold storage in UW solution.

Material and Methods

Animal Preparation and Reagents

Hearts were obtained from male Sprague-Dawley rats weighing 250 to 300 g and maintained on a standard laboratory diet. 5-Hydroxytryptamine and sodium nitroprusside (SNP) were obtained from Sigma Chemicals Ltd, St. Louis. Crystalloid cardioplegia was obtained from the Montreal Heart Institute pharmacy and UW solution, from Dupont Pharma, Toronto (Table 1). All animals were cared for in compliance with the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH publication No. 85-23, revised 1985).

Perfusion Technique

The rats were heparinized (3 mg/kg) and decapitated. The chest was immediately opened, and the aorta was isolated, cannulated, and perfused in vivo with 37°C oxygenated (95% O₂ and 5% CO₂) Krebs-Ringer solution ([mmol/L]: NaCl, 118.3; KCl, 4.7; MgSO₄, 1.2; KH₂PO₄, 1.22; CaCl₂, 1.3; NaHCO₃, 25.0; and glucose, 15; pH 7.4 at 37°C). The perfused hearts were excised from the chest

and mounted onto a modified Langendorff apparatus [20]. Using this harvesting technique, myocardial ischemia was kept to less than 45 seconds. The perfusion pressure was maintained at 80 cm H₂O. The hearts were atrially paced at 300 to 350 beats per minute. The maximum left ventricular pressure and rate of change of LVP (dP/dt) were measured by inserting a latex balloon inside the left ventricle through the left atrium and inflating it to maintain a left ventricular end-diastolic pressure of 10 mm Hg. Left ventricular pressure was measured with a Gould transducer signal conditioner (Gould 20-4615-50), and dP/dt was recorded using a Gould differentiator signal conditioner (Gould 13-G4615-71). The mean and pulsatile coronary flows were measured using a 2-mm factory-precalibrated cannulating ultrasonic probe (Transonic cannulating flow probe type 2N; internal diameter, 3.2 mm; resolution, 0.1 mL/min; Transonic Systems Inc) to which the aorta was attached. Two hearts were studied simultaneously in two Langendorff apparatuses and all data recorded on an eight-channel Gould recorder.

Drugs were dissolved in Krebs-Ringer solution and perfused with a Harvard syringe infusion pump 22 (Harvard Apparatus) to assure a constant drug delivery (5HT, 10⁻⁶ mol/L; SNP, 10⁻⁵ mol/L) during coronary perfusion.

Protocol

After harvesting, hearts were perfused and stabilized for a period of 30 minutes in the Langendorff apparatus. At the end of this period, coronary flow, dP/dt, and LVP were recorded for baseline values. Then 5HT and SNP were sequentially infused into the rat aorta through the cannula for 4 minutes each. Changes in coronary flow were recorded at the end of the 4-minute infusion. Each drug infusion was followed by a 30-minute washout period to allow the coronary flow to return to control values. The drugs were always administered in the same sequence, 5HT first followed by SNP 30 minutes later...

After these steps, hearts were exposed to perfusion with and storage in different cardioplegic solutions as described in the Experimental Design section. This was followed by a 30-minute recovery period, during which hearts were reperfused with 37°C Krebs-Ringer solution at a perfusion pressure of 80 cm H₂O. Coronary flow, dP/dt, and LVP were recorded at the end of the recovery period. Hearts then underwent 5HT and SNP infusion again and changes in coronary flow were recorded as previously described.

Experimental Design

PART I. The first set of experiments was designed to assess coronary endothelial function after a short perfusion with UW solution or CHCS. In group 1 (n = 6), hearts were perfused with 4°C CHCS at 80 cm H₂O pressure for 10 minutes. In group 2 (n = 6), hearts were perfused with UW solution at the same pressure and for the same time. In group 3 (n = 6), hearts were exposed to 10 minutes of warm ischemia by cross-clamping the cannula just above the perfused aorta. This group served as the controls to measure the effect of warm ischemia alone.

PART II. The second set of experiments was specifically designed to assess endothelium-dependent coronary artery relaxation after long-term preservation. Hearts in group 4 ($n = 6$) were first perfused with 4°C CHCS (perfusion pressure, 80 cm H₂O; perfusion time, 10 minutes) to induce myocardial arrest and then preserved for 4 hours in the same solution (4°C). Hearts in group 5 ($n = 6$) were similarly arrested with UW solution perfusion and stored in the same solution for 4 hours. Hearts in group 6 ($n = 6$) were stored in an isotonic solution (0.09% NaCl) for 4 hours at 4°C. In this group, unlike groups 4 and 5, the solution was not allowed to get in physical contact with the coronary endothelium (the aortic cannula was kept cross-clamped). This was done specifically to evaluate the effect of topical cooling alone.

Data Analysis

Baseline flow is recorded in milliliters per minute. Changes in coronary artery flow before and after exposure to perfusion with and storage in the different solutions are reported as percent change versus the baseline value. All data are expressed as the mean $\pm$ the standard deviation. Statistical analysis was performed with Student's paired t test. The significance of differences was established at 95% ($p < 0.05$).

Results

Part I (Perfusion Alone)

ENDOTHELIAL AND SMOOTH MUSCLE RESPONSIVENESS. Group 1 hearts perfused with CHCS reacted similarly to 5HT and SNP infusion both before and after perfusion, indicating that muscle tone and endothelial reactivity were still present and not affected by the perfusion (Fig 1).

The group 2 hearts were perfused with UW solution. The perfusion significantly reduced the 5HT-induced coronary relaxation ($35\% \pm 10\%$ versus $13\% \pm 10\%$), indicating severe endothelial dysfunction (see Fig 1A). Coronary vasodilatation after SNP infusion was also diminished, indicating some decrease in smooth muscle responsiveness ($79\% \pm 19\%$ versus $62\% \pm 6\%$; $p = 0.06$) (see Fig 1B).

Group 3 was not exposed to any specific preservation solution but did have a warm ischemic period of 10 minutes. The coronary responsiveness to 5HT infusion was decreased to a certain extent ($35\% \pm 8\%$ versus $24\% \pm 7\%$; $p =$ not significant), whereas coronary flow response to SNP remained unaffected ($67\% \pm 22\%$ versus $66\% \pm 22\%$) (see Fig 1).

CORONARY FLOW. Coronary flow was significantly reduced in group 1 after CHCS perfusion (Table 2). It remained unaffected in groups 2 and 3.

GLOBAL HEART FUNCTION. Left ventricular systolic pressure and dP/dt remained unchanged throughout this part of the study (Table 3).

Part II (Perfusion and Storage)

ENDOTHELIAL AND SMOOTH MUSCLE RESPONSIVENESS. In group 4, hearts were arrested with 10-minute perfusion

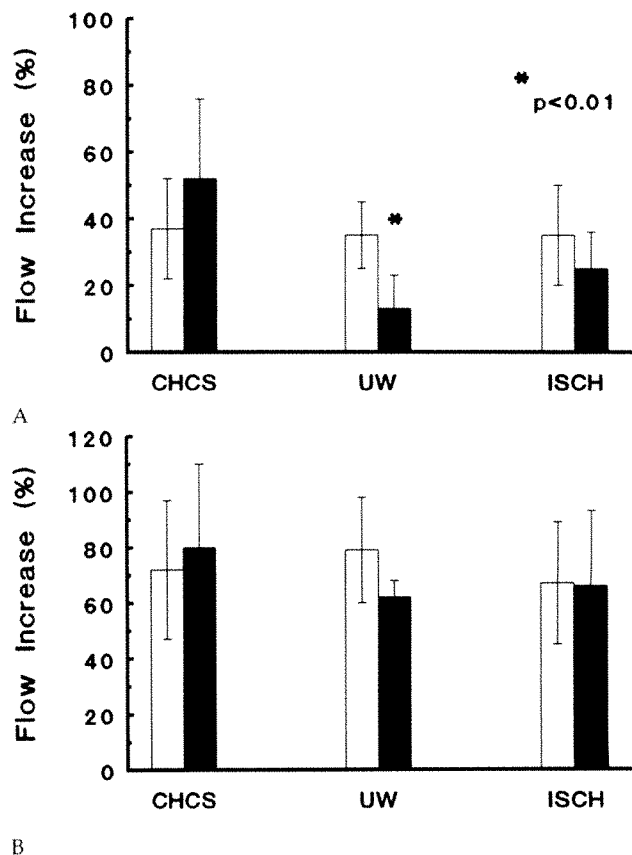


Fig 1. Percent increase in coronary flow induced by (A) 5-hydroxytryptamine (10^{-6} mmol/L) and (B) sodium nitroprusside (10^{-5} mmol/L) before (open bars) and after (solid bars) 10-minute perfusion with 4°C crystalloid hyperkalemic cardioplegic solution (CHCS) or University of Wisconsin solution (UW) or after 10 minutes of warm ischemia (ISCH).

and stored in CHCS. Vascular endothelial and smooth muscle functions were not significantly affected after storage (Fig 2).

Group 5 hearts perfused with and stored in UW solution showed severe impairment of 5HT-induced coronary artery vasodilatation ($34\% \pm 5\%$ versus $-5\% \pm 12\%$; $p < 0.01$) and a significant decrease in smooth muscle response to SNP ($84\% \pm 35\%$ versus $30\% \pm 15\%$; $p < 0.05$) (see Fig 2).

Table 2. Baseline Coronary Artery Flow at the Beginning of the Experiment and After the Recovery Period

Group	Baseline Flow (mL/min)		p Value
	Before	After	
1	6.7 $\pm$ 0.8	5.4 $\pm$ 1.0	<0.05
2	10.0 $\pm$ 1.5	10.0 $\pm$ 2.1	NS
3	6.8 $\pm$ 0.3	6.2 $\pm$ 0.5	NS
4	7.6 $\pm$ 1.4	5.3 $\pm$ 0.7	<0.01
5	6.3 $\pm$ 1.0	6.3 $\pm$ 2.9	NS
6	6.9 $\pm$ 0.6	6.3 $\pm$ 1.4	<0.01

NS = not significant.

Table 3. Rate of Rise of Left Ventricular Pressure and Left Ventricular Pressure at the Beginning of Experiment and After Recovery Period

Group	dP/dt (mm Hg/s)		LVP (mm Hg)	
	Before	After	Before	After
1	1,450 ± 150	1,425 ± 458	65 ± 5	56 ± 11
2	1,240 ± 600	1,160 ± 600	62 ± 19	46 ± 15
3	1,880 ± 450	1,900 ± 500	77 ± 20	81 ± 24
4	1,900 ± 580	1,500 ± 390	70 ± 17	57 ± 10
5	1,500 ± 370	775 ± 735 ^a	67 ± 10	35 ± 20 ^b
6	1,120 ± 500	1,080 ± 600	63 ± 12	59 ± 13

^aSignificance: $p = 0.06$.

^bSignificance: $p < 0.05$.

dP/dt = rate of change of left ventricular pressure; LVP = left ventricular pressure.

Group 6 hearts had 4 hours of cold ischemia without cardioplegic arrest and displayed a significant decrease in 5HT-induced coronary artery response ($60\% \pm 23\%$ versus $24\% \pm 12\%$; $p < 0.01$). Smooth muscle response was not affected ($72\% \pm 18\%$ versus $80\% \pm 35\%$) (see Fig 2).

CORONARY FLOW. Coronary flow was significantly affected in groups 4 and 6 (see Table 2). Only hearts perfused and stored in UW solution were not affected.

GLOBAL HEART FUNCTION. There was a decrease in LVP (70 ± 9 mm Hg versus 35 ± 19 mm Hg; $p < 0.05$) and dP/dt ($1,525 \pm 370$ mm Hg/s versus 775 ± 700 mm Hg/s; $p = 0.06$) in hearts preserved with UW solution (see Table 3). Topical cooling alone and storage in 4°C CHCS did not alter global heart function.

Comment

These experiments demonstrate that perfusion with and storage in different preservation solutions could be detrimental to the endothelium-dependent coronary artery relaxation of the isolated rat heart. A normal endothelial capacity to release EDRFs is essential to assure optimal graft preservation during heart transplantation by protecting coronary vessels against vasospasm and thrombi formation during reperfusion [21, 22]. There is also experimental evidence that once the endothelium is made dysfunctional (subsequent to ischemic or mechanical injury), it does not resume normal function; rather, such injury leads to chronically increased vascular tone [13, 14, 16] and can also contribute to early atherosclerosis [23].

5-Hydroxytryptamine was chosen to evaluate coronary endothelial function in this model because 5HT has been shown to stimulate coronary artery relaxation through nitric oxide release in the rat [24]. In these conditions, 5HT activates endothelium-dependent serotonergic receptors and releases nitric oxide, which relaxes the smooth muscle by increasing cyclic guanosine monophosphate [25]. Sodium nitroprusside relaxes smooth muscle by increasing the content of cyclic guanosine monophosphate in vascular smooth muscle through an endotheli-

um-independent pathway, and its action can be preserved even when the endothelium is dysfunctional [25].

In this study, we have shown that perfusion with or without subsequent storage in a pH-balanced CHCS containing 24 mmol of KCl per liter creates minimal endothelial and smooth muscle damage when the infusion pressure is kept at 80 cm H₂O and infusion time is limited to 10 minutes. A short perfusion with UW solution was found to cause more damage to coronary artery endothelial responsiveness than ischemia alone. The combination of perfusion and 4-hour storage was even more detrimental to endothelial function. Baseline coronary flow was affected in hearts perfused with and stored in CHCS and also in those stored for 4 hours without preservation solution after cold ischemia alone. Perfusion with and storage in UW solution did not affect baseline coronary flow.

Global heart function as evaluated by LVP and dP/dt was affected only in hearts perfused with and preserved in UW solution. This finding indicates that the ischemic periods (10 minutes and 4 hours) used in these experiments were not responsible for altering global heart function.

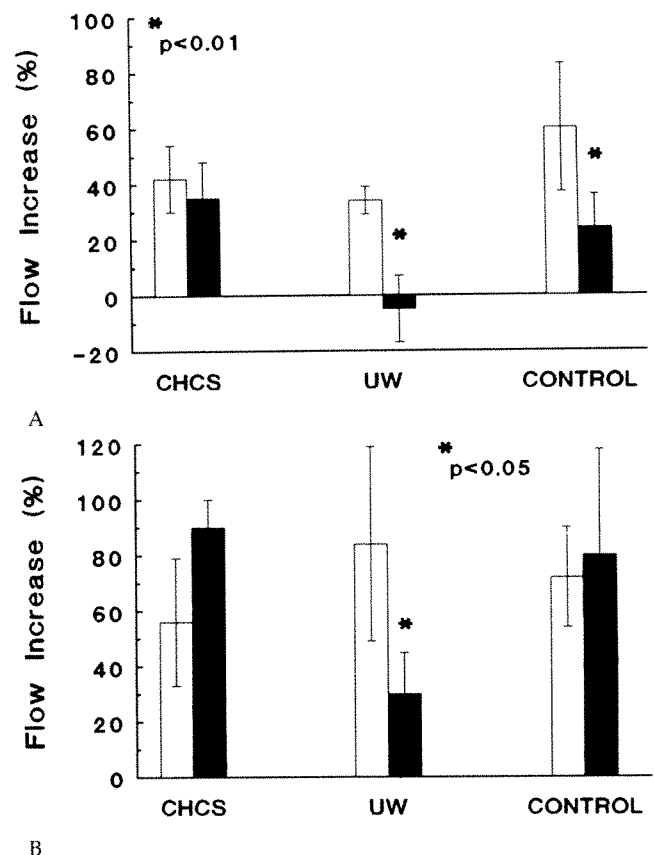


Fig 2. Percent increase in coronary flow induced by (A) 5-hydroxytryptamine (10^{-6} mmol/L) and (B) sodium nitroprusside (10^{-5} mmol/L) before (open bars) and after (solid bars) 10-minute perfusion with and 4-hour cold (4°C) storage in crystalloid hyperkalemic cardioplegic solution (CHCS) or University of Wisconsin (UW) solution or 4 hours of topical cooling alone (CONTROL).

The formulation of UW solution was designed to address several theoretical and practical concerns. Various components are added to decrease cellular acidosis and swelling, prevent free radical-mediated reperfusion injury, stabilize membranes, and facilitate adenosine triphosphate regeneration [6]. The solution contains a high K^+ and low Na^+ concentration, and two nonmetabolized, osmotically active large molecular agents, potassium lactobionate and the saccharide raffinose [26, 27]. These prevent cellular swelling caused by anaerobic, hypothermic-induced Na-K ATPase suppression and prevent sodium and chloride from entering the cell [28]. All these components may affect the endothelium.

Potassium in CHCS has been blamed for causing endothelial functional alteration [16, 17]. Nevertheless, we [19] have established that a high KCl concentration (100 mmol/L) could be used in conjunction with CHCS provided perfusion pressure was kept to 80 cm H_2O and infusion time to 10 minutes. The potassium concentration is probably not the only factor responsible for endothelial damage. The osmotically active, large-molecule agents and the hydroxyethyl starch (Pentastarch) used in the UW solution increase its viscosity compared with standard cardioplegia. This higher viscosity (observed after we found the Langendorff apparatus extremely hard to clean after the experiment) combined with the hydrostatic pressure of the perfusion increases intravascular shear stress and can potentially damage the endothelium.

In certain experimental conditions, storage in UW solution has been shown to preserve nitric oxide production, cell morphology, adenosine triphosphate levels, and viability of artificially grown endothelial cells [29, 30]. The experimental designs of these studies depart substantially from the design used in our model. In these studies, endothelial cells were not subjected to any specific hemodynamic variables such as infusion velocity or hydrostatic pressure. In the isolated rat heart model, changes in coronary flow result from variation in resistance arterioles, which are small-diameter vessels. Energy losses associated with fluid flow are mainly related to the viscosity of the fluid and its inertia. Because energy losses are inversely proportional to the fourth power of the radius, the endothelial cells of coronary arterioles are more susceptible to damage by high shear stress when the viscosity of the solution is increased [31].

In Figure 3, a sample of the coronary flow changes observed during CHCS and UW solution perfusion is displayed. The top part of the figure represents flow changes during CHCS perfusion. Flow acutely increases as perfusion starts and slowly returns to the preinfusion level. This flow increase, even though the perfusion pressure was kept constant, can be caused by the lower temperature of the cardioplegic solution. Lowering the temperature has been shown to augment the sensitivity of vascular smooth muscle to EDRFs in the rat [32]. Contrary to that, during cold UW perfusion (bottom part), coronary flow decreases sharply at the very beginning, rapidly increases to half the level of the preinfusion flow, and returns to normal only when perfusion is completed. This suggests an acute increase in vascular resistance possibly

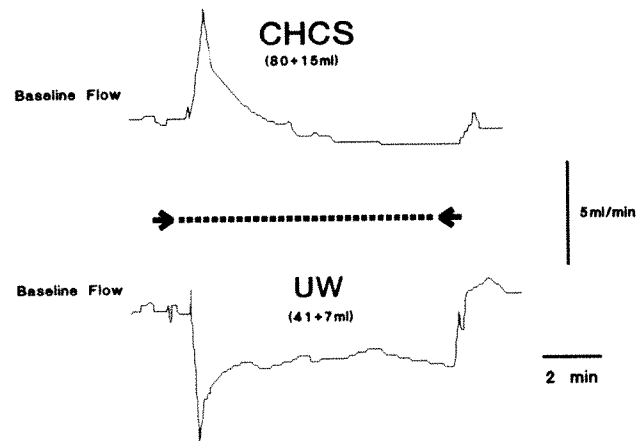


Fig 3. Baseline flow pattern during perfusion with crystalloid hyperkalemic cardioplegic solution (CHCS) or University of Wisconsin solution (UW). Broken line represents the period of solution perfusion. See Comment section for explanation.

caused by high KCl content or flow obstruction related to fluid viscosity.

The amount of solution given during the 10-minute perfusion period was significantly higher in the CHCS group, which confirms the lower vascular resistance in this group (80 ± 15 mL versus 41 ± 7 mL; $p < 0.01$). This could explain part of the endothelial injury related to the UW solution. Interestingly, baseline flow was not affected in the UW solution-preserved hearts. The reason for this is unclear. Coronary flows in hearts perfused with and stored in CHCS or just stored without any preservation solution were consistently decreased after storage, a finding suggesting a reduction in baseline EDRF release even though the EDRF release to a 5HT bolus was preserved. Despite the fact that coronary flow was significantly lowered during UW perfusion, this effect was not sustained.

In regard to global heart function, our results differ from those obtained in other experimental and human studies. Part of the explanation may come from oxidized glutathione, present in aged shelf-stored UW solution. Oxidized glutathione has been associated with decreased efficiency in heart preservation [33]. Reduced glutathione is added to chemically reduce cytotoxic oxidants and suppress lipid peroxidation [6]. With time, it converts to its oxidized form, which is an efficient activator of the collagenolytic system, both in vitro and in vivo, causing structural damage during long-term preservation [34-36]. The UW solution used in this study was not freshly prepared but shelf stored, following the manufacturer's recommendations and used with respect to the expiration date. The amount of oxidized glutathione was not measured. Moreover, the acalcemic composition of the UW solution has also been found to cause calcium paradox-related myocyte injury during reperfusion [8]. As the Krebs solution used in our experiment contains calcium, it may have contributed to reperfusion injury. All these factors may explain the nonoptimal vascular smooth muscle and myocyte preservation observed in this study.

In conclusion, this study highlights interesting points regarding endothelial vascular function in myocardial protection. Extracellular-formulated solutions with buffer capability and osmotically active agents seem to offer good functional preservation of myocyte and coronary artery endothelial reactivity. In regard to UW solution employed either as a cardioplegic or preservation solution, further investigation is needed before its use in human heart transplantation can be recommended, as endothelium-dependent coronary relaxation was poorly preserved. Efforts to improve myocardial protection should consider endothelial preservation as much as myocyte preservation.

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DISCUSSION

DR IRVING L. KRON (Charlottesville, VA): I agree entirely with your conclusions in the animal model. At the recent American Heart Association meeting, my colleagues and I presented some work using an isolated vascular ring model in rabbits and found the exact same effect. How do you explain the paradox that some clinical investigators have noted excellent preservation with UW solution?

DR CARTIER: This is a good question. Investigators who reported good results used a cultured cell model in which endothelial cells are grown on microcarrier beads and then exposed to UW solution. In that model without a vascular network, the endothelial cells are not subjected to the same hydrostatic pressure and shear stress conditions. The results cannot be compared. Furthermore, we did not use freshly made UW solution but the commercially available one currently used for liver transplantation. The reduced glutathione contained in the shelf-stored solution could be responsible for the poor preservation seen in our model.

DR AXEL HAVERICH (Hannover, Germany): I very much enjoyed this presentation because it highlights some problems about the high potassium concentration in the UW solution. My associates and I were very concerned about the potassium concentration before we performed our prospective, randomized clinical trial comparing UW solution and St. Thomas' Hospital solution for cardioplegia in patients undergoing heart transplantation.

Because of our concerns, we measured coronary flow and coronary vascular resistance at 5 and 10 minutes' reperfusion of the transplanted hearts after a mean ischemic time of 150 minutes. Surprisingly, we did not find the same results that you presented in your experimental study. There was no difference in coronary flow or coronary vascular resistance between UW-preserved hearts and hearts preserved with St. Thomas' Hospital solution. Also, there was much better recovery of electrical function in the donor hearts, and at 1 day, 2 days, and 4 days after transplantation, left ventricular function and right ventricular function were comparable in the two groups. There was no difference in regard to these indices when comparing UW solution and St. Thomas' Hospital solution.

DR CARTIER: This is an interesting point. I did not comment about baseline coronary flow in the presentation. When we measured baseline coronary flow before and after perfusion with UW solution or regular cardioplegic solution, we did not find any significant difference between solutions. Changes were observed only when we looked for endothelium-derived relaxing factor production by the coronary endothelium. In our model, the endothelium-dependent coronary vasorelaxation was severely

impaired in hearts perfused with or perfused with and stored in UW solution. Simply looking at baseline coronary flow does not allow any conclusion about vascular endothelial preservation.

DR JAMES C. STRINGHAM (Madison, WI): I am very interested in your results, particularly in light of the data I presented previously, because my associates and I also found a loss of coronary flow, even when hearts functioned very well. I think your point about shear stress is a good one, especially in small hearts like that of the rabbit or the rat. In our study, we found that rabbit hearts perfused at a pressure of 80 or 100 cm H₂O did not function well, and we actually had to lower perfusion pressure to 50 cm H₂O to get them to function better. So I think that may be an important point and may explain why some of the microvasculature seems to be damaged.

I also think your point about potassium is a good one. This continues to be a challenge and a controversy when using UW solution in the heart, and the potassium concentration may have to be lowered. Did you ever try using a UW solution with an altered potassium concentration, or did you try using a decreased coronary perfusion pressure in your model?

DR CARTIER: These are interesting comments. We have not tried using UW solution with a lower potassium concentration. However, we have shown in a previous study that potassium used in conjunction with regular cardioplegic solution could be infused at a very high concentration (100 mmol/L) without endothelial damage provided perfusion pressure and duration of perfusion were limited. We found that these conditions were a perfusion pressure of 80 cm H₂O and a perfusion period of 10 minutes. Increasing the perfusion pressure to 160 cm H₂O completely destroyed the endothelial responsiveness. Then potassium concentration is probably an important factor, although maybe not as much as viscosity and shear stress at the microvascular level. Trying the same experiments at a lower perfusion pressure is an excellent suggestion.

DR ADNAN COBANOGLU (Portland, OR): Dr Cartier, how about the osmolality of the UW solution? There are some data from the Hershey group that as osmolality is reduced, preservation, both functional and biochemical, is better.

DR CARTIER: That is a good point. The osmolality of the UW solution is 320 mosm/L, which is not very high. If you want to reduce it, you have to remove components of the solution, and the question is, which ones are we going to remove? We did studies using a solution with an osmolality approaching 500 mosm/L, and again, endothelial damage was related to high (160 cm H₂O) perfusion pressure. However, we did not study long-term preservation with these solutions.

Cerebral Metabolism and Circulatory Arrest: Effects of Duration and Strategies for Protection

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Hypothermic total circulatory arrest (CA) is commonly used to facilitate repair of complex congenital heart defects. However, the "safe" period of CA remains to be defined. Extended periods of hypothermic total circulatory arrest may impair cerebral metabolism and cause ischemic brain injury. This study defines the relationship between increasing durations of CA at 18°C and cerebral metabolism, and examines the protective value of topical cooling of the head or continuous "trickle" flow (5 to 10 mL · kg⁻¹ · min⁻¹). Thirty-three 1-week-old piglets were randomized to six experimental groups: control; 15, 30, or 60 minutes of CA; 60 minutes of CA with topical cooling of the head; and 60 minutes of trickle flow. Animals were placed on cardiopulmonary bypass (CPB) at 100 mL · kg⁻¹ · min⁻¹ and cooled to 18°C. After the experimental period of CA or trickle flow (or 60 minutes of CPB at normal flow for the control

group), animals were rewarmed to 37°C and weaned from CPB. Data were obtained before and immediately after CPB at 37°C, and before and immediately after the experimental period at 18°C. Parameters measured included cerebral blood flow by xenon 133 clearance, arterial and sagittal sinus blood gases, and cerebral metabolism. Hypothermic total circulatory arrest caused an impairment of cerebral metabolism that was directly proportional to CA duration ($r^2 = 0.73$; $p = 0.0001$), and recovery of metabolic function after 60 minutes of CA improved more than 50% if the head was packed in ice. If technically feasible, CPB flow of only 5 to 10 mL · kg⁻¹ · min⁻¹ during hypothermia is superior to CA with respect to cerebral protection. Future studies with this model can be used to develop optimal modes of cerebral protection during neonatal heart operations.

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Deep hypothermic circulatory arrest (CA) is an intraoperative technique commonly used during repair of congenital heart lesions. The theoretical basis for the use of total CA for cardiac operations is that a "safe" duration exists, the length of which is inversely proportional to the temperature of the organism during the arrest period [1]. In clinical practice, a short period of hypothermic CA is considered to be well-tolerated. Conversely, durations of CA extending beyond some safe limit are thought to cause cerebral ischemia and brain injury. However, these time points are poorly defined, and it is more likely that a spectrum of effects occurs between the two extremes. Better characterization of the pattern of response to CA will facilitate objective evaluation of current techniques and the development of new methods of cerebral protection.

This study was conducted with two objectives: (1) to define the pattern of cerebral response to increasing durations of hypothermic CA and (2) to evaluate two commonly employed strategies (topical cooling of the head and "trickle flow" bypass) that may alter this response and thereby provide a longer period of safety for operative repairs. The protocol and techniques used in

this investigation were designed to duplicate those used in the routine clinical setting.

Material and Methods

Animal Preparation

All animal experiments were conducted with the approval of the institution's Animal Care and Use Committee and received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH publication No. 85-23, revised 1985). Thirty-three 1-week-old piglets (2 to 3 kg) were preanesthetized with ketamine (20 mg/kg), intubated, and mechanically ventilated (Infant Ventilator; Sechrist Industries, Anaheim, CA). Animals were paralyzed with pancuronium (0.1 mg/kg), and anesthesia was maintained by a continuous fentanyl infusion (50 µg · kg⁻¹ · h⁻¹). Nasopharyngeal and rectal temperature probes were placed and a femoral artery catheter was inserted for continuous blood pressure monitoring and arterial blood gas sampling. Animals then underwent median sternotomy. Cardiac instrumentation consisted of a left atrial catheter for xenon 133 injection, a pulmonary artery catheter for mixed-venous blood gas sampling, and an 8-mm flow probe (Transonic Systems, Ithaca, NY) positioned around the pulmonary artery for measurement of cardiac output.

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Measurement of Cerebral Blood Flow

Cerebral blood flow (CBF) was determined by the xenon (^{133}Xe) clearance technique. Two brass-insulated cadmium telluride gamma emission detectors (approximately 1 cm in diameter) were positioned extracranially over the right and left temporal lobes. Xenon (1.5 mCi in 2 mL of normal saline solution) was injected into the arterial circulation through the left atrial catheter (or through the aortic cannula during cardiopulmonary bypass [CPB]). Radioactive decay was recorded separately from each hemisphere over 15 minutes. Cerebral blood flow was then derived from the radioactive decay curves using a modification of the initial slope index method [2] as follows: $\text{CBF} = (\text{slope})(\lambda)(100)$, where slope is the natural logarithm of the ^{133}Xe clearance curve 1 minute after the injection peak, λ is the tissue-blood partition coefficient for xenon, corrected for hematocrit and temperature [3], and 100 is for conversion of units from $\text{mL} \cdot \text{g}^{-1} \cdot \text{min}^{-1}$ to $\text{mL} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$. Cerebral blood flow was determined for each cerebral hemisphere and averaged to derive the global CBF.

Measurement of Cerebral Metabolism

At each stage of the experiment, sagittal sinus blood was sampled through the midline sagittal suture. The cerebral arteriovenous oxygen content difference (cer Ca-vO_2) was then calculated as $\text{CaO}_2 - \text{CvSO}_2$, where CaO_2 is arterial oxygen content and CvSO_2 is the sagittal sinus oxygen content. Blood gases were measured by a GEM-STAT Blood Gas/Electrolyte Monitor (Mallinckrodt, Ann Arbor, MI). After measurement of CBF by xenon clearance, cerebral metabolism (CMRO_2), cerebral oxygen delivery (cer DO_2), and cerebral oxygen extraction ratio (cer O_2 Ext Ratio) were calculated as follows:

$$\text{CMRO}_2 (\text{mL O}_2 \cdot 100 \text{ g brain}^{-1} \cdot \text{min}^{-1})$$

$$= (\text{cer Ca-vO}_2)(\text{CBF})$$

$$\text{cer DO}_2 (\text{mL O}_2 \cdot 100 \text{ g brain}^{-1} \cdot \text{min}^{-1})$$

$$= (\text{CaO}_2)(\text{CBF});$$

$$\text{cer O}_2 \text{ Ext Ratio} = \text{CMRO}_2 / \text{cer DO}_2.$$

Cardiopulmonary Bypass Technique

The CPB circuit consisted of a Stöckert-Shiley (Irvine, CA) CAPS nonpulsatile roller pump and a Cobe VP-CML (Denver, CO) membrane lung with venous reservoir. A CDI-300 (CDI; 3M Healthcare, Irvine, CA) continuous in-line blood gas analyzer was used on the arterial and venous limbs to precisely control circuit blood gases. The circuit prime consisted of fresh donor pig whole blood with a hematocrit ranging from 0.22 to 0.26. After heparinization (1,000 U/kg), 8F arterial and 14F venous cannulas were placed in the aortic root and right atrium, respectively. Cardiopulmonary bypass before and after the experimental period was maintained at $100 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ to duplicate the normal cardiac output of the piglet. Blood pressure was allowed to vary without intervention. Circuit blood gases were managed according to the alpha-stat protocol

[4] and maintained pH at 7.35 to 7.40 and carbon dioxide tension at 35 to 40 mm Hg, uncorrected for temperature.

Experimental Protocol and Data Collection Sequence

Data collection was divided into four stages (Fig 1). Data first were collected at 37°C immediately before cannulation for CPB (Pre). After cannulation and initiation of CPB at $100 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and 37°C , animals were cooled by perfusion over 30 minutes to 18°C pharyngeal temperature and the first hypothermia data were collected (HT1). Animals were then randomized to one of six experimental groups as described in Figure 1. Animals in the control group were cooled to 18°C and maintained on CPB at $100 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for 60 minutes without any period of CA. Three groups of animals underwent CA at 18°C for durations of either 15, 30, or 60 minutes. Two cerebral protection strategies were also tested: 60 minutes of CA with the head packed in ice during the CA period, and continuous CPB at 5 to $10 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ at 18°C for 60 minutes. Upon completion of the respective experimental period, CPB was reinstituted at $100 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and 18°C and data were collected after stabilization for 10 minutes (HT2). Animals were then rewarmed to a pharyngeal temperature of 37°C and weaned from CPB. Measurements were taken immediately after hemodynamic and ventilatory stability was achieved (approximately 30 minutes after CPB) (Post). Data collection at each of these stages consisted of pharyngeal and rectal temperatures; heart rate; blood pressure; cardiac output; pump flow; arterial, sagittal sinus, and pulmonary artery blood gases; hematocrit; electrolytes; ionized calcium; and CBF. In addition to cerebral oxygen delivery and metabolism, total systemic oxygen consumption and systemic oxygen extraction ratio were calculated by the Fick equation using cardiac output with arterial and mixed-venous blood gases.

Statistical Analysis

Data were collated and statistically analyzed using the paired *t* test to compare Pre versus Post CPB and HT1 versus HT2 results for each experimental group. Post CPB results were compared between groups using analysis of variance. Statistical significance was tested at the 95% confidence level. All results are expressed as the mean value $\pm$ the standard error of the mean.

Results

All animals completed each stage of the study successfully. Total study time from induction of anesthesia to Post data collection was 4 ± 0.5 hours depending on experimental group.

General Effects of Hypothermia

Pre and HT1 values for all animals are listed in Table 1. As compared with Pre values at normothermia, perfusion cooling to 18°C caused significant reductions in heart rate, CMRO_2 , cerebral oxygen extraction ratio, and systemic oxygen consumption. However, despite cooling over 30 minutes, CMRO_2 was reduced by only $56.5\% \pm 3.7\%$ in

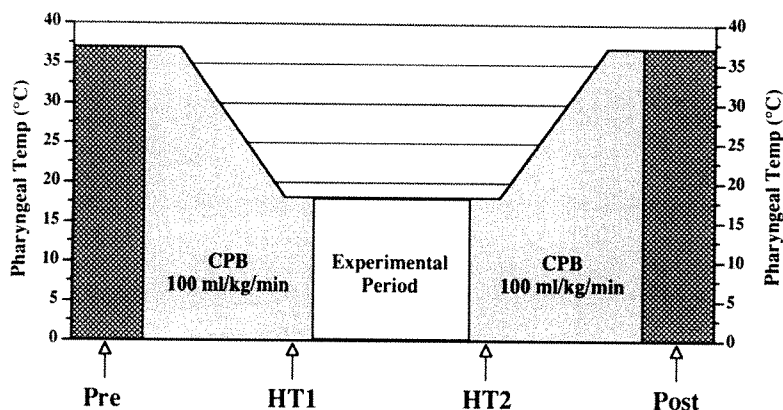


Fig 1. Experimental protocol and data collection sequence: After anesthesia and instrumentation was accomplished, baseline (Pre) measurements were obtained. Animals were then cannulated and placed on cardiopulmonary bypass (CPB) at $100 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and 37°C , then perfusion-cooled to 18°C over 30 minutes. Data were obtained on full CPB immediately before the experimental period (HT1) and after the experimental period (HT2) on full CPB. The groups studied during the experimental period were as follows: (1) Control 18°C CPB at $100 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for 60 min ($n = 5$); (2) 15 minutes of total circulatory arrest at 18°C (15°CA ; $n = 5$); (3) 30 minutes of total circulatory arrest at 18°C (30°CA ; $n = 6$); (4) 60 minutes of total circulatory arrest at 18°C (60°CA ; $n = 6$); (5) 60 minutes of total circulatory arrest with cerebral topical cooling (60°CA-TC ; $n = 6$); and (6) 60 minutes of trickle-flow CPB at 5 to $10 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (60°TF ; $n = 5$). Animals were then rewarmed to 37°C and weaned off CPB. Final measurements were obtained after stabilization for 30 minutes (Post).

all animals. In the experimental groups that were subjected to CA, the CMRO_2 immediately before initiation of CA averaged $41.8\% \pm 4.2\%$ of baseline oxygen requirements. Systemic and cerebral arteriovenous oxygen content differences decreased with cooling, whereas mean arterial pressure, systemic perfusion, cerebral blood flow, and cerebral oxygen delivery were not statistically different.

Effects of Circulatory Arrest and Protective Measures on Cerebral Metabolism During Hypothermic Perfusion

Upon completion of the experimental period (HT2) and reinstitution of CPB at $100 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and 18°C , the effects of CA and cerebral protective methods were recorded and are listed in Table 2. Compared with HT1 values, CMRO_2 at HT2 was significantly impaired in groups receiving 15, 30, or 60 minutes of CA, whereas pharyngeal temperatures and CBF were unchanged. Top-

ical cooling of the head during 60 minutes of CA significantly reduced pharyngeal temperature to an average of $12.6^\circ \pm 1.4^\circ\text{C}$, and CMRO_2 was fully recovered. Trickle flow for 60 minutes also sustained CMRO_2 , which was significantly greater when compared with values in the CA groups at HT2.

Effects of Circulatory Arrest on Cerebral Metabolism After Weaning From Cardiopulmonary Bypass

Pre and Post CPB values for several indices of cerebral metabolism are listed in Table 3. In control animals, all indices returned to baseline values, and hypothermic CPB demonstrated no measurable effect on CMRO_2 after re-warming. In the groups subjected to a period of CA, CMRO_2 was significantly impaired when compared with Pre values within each group, as well as when compared with the control Post values between groups. When expressed as a percent recovery of Pre values, impairment

Table 1. Selected Parameters at Pre and HT1 for All Animals ($n = 33$)

Parameter	Pre	HT1
Pharyngeal temperature ($^\circ\text{C}$)	36.2 ± 0.2	17.3 ± 0.2^a
Rectal temperature ($^\circ\text{C}$)	36.7 ± 0.2	18.8 ± 0.2^a
Heart rate (beats/min)	154 ± 7	16 ± 4^a
Mean arterial pressure (mm Hg)	61 ± 2.8	66 ± 4
Hematocrit	0.32 ± 0.01	0.27 ± 0.01^a
Cardiac output ($\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$; CPB for HT1)	97 ± 36	100 ± 0
Cerebral blood flow ($\text{mL} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$)	24.5 ± 1.6	25.3 ± 1.3
Cerebral a- vO_2 difference (mL/dL)	8.8 ± 0.3	3.6 ± 0.3^a
CMRO_2 ($\text{mL} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$)	1.98 ± 0.06	0.84 ± 0.07^a
Cerebral DO_2 ($\text{mL} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$)	3.69 ± 0.24	3.54 ± 0.19
Cerebral O_2 extraction ratio	0.58 ± 0.03	0.25 ± 0.02^a
Systemic oxygen consumption ($\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)	5.24 ± 0.24	1.78 ± 0.21^a

^a $p < 0.05$ versus Pre.

a- vO_2 = arteriovenous oxygen content; CMRO_2 = cerebral metabolism; DO_2 = oxygen delivery.

Table 2. Cerebral Response to Circulatory Arrest and Protective Measures at Hypothermia

Group ^a	Pharyngeal Temperature (°C)		CBF (mL · 100 g ⁻¹ · min ⁻¹)		CMRO ₂ (mL · 100 g ⁻¹ · min ⁻¹)	
	HT1	HT2	HT1	HT2	HT1	HT2
Control ^b	17.5 ± 0.4		25.55 ± 1.43		0.68 ± 0.11	
15'CA	17.6 ± 0.4	18.2 ± 0.9 ^c	21.97 ± 2.56	23.24 ± 1.00	0.85 ± 0.16	0.43 ± 0.02 ^{d,*}
30'CA	17.4 ± 0.5	18.2 ± 0.9 ^c	29.38 ± 5.47	33.59 ± 4.84	1.02 ± 0.11	0.35 ± 0.05 ^{d,*}
60'CA	17.3 ± 0.7	18.0 ± 0.7 ^c	21.52 ± 2.18	24.24 ± 3.12	0.79 ± 0.14	0.42 ± 0.07 ^{d,*}
60'CA-TC	16.0 ± 0.5	12.6 ± 1.4 ^d	26.67 ± 2.3	30.11 ± 2.65	0.58 ± 0.11	0.72 ± 0.17
60'TF	18.0 ± 0.0	18.0 ± 0.0 ^c	26.82 ± 1.93	23.61 ± 1.37	1.15 ± 0.28	1.05 ± 0.31

^a Groups are defined in Figure 1. ^b In control animals, values represent measurements obtained midway during 60 minutes of full cardiopulmonary bypass at 18°C. ^c $p < 0.05$ versus 60'CA-TC-HT2 by analysis of variance. ^d $p < 0.05$ versus HT1 by paired t test. ^e $p < 0.05$ versus 60'TF-HT2 by analysis of variance

CBF = cerebral blood flow; CMRO₂ = cerebral metabolic rate of oxygen.

of CMRO₂ directly correlated with the duration of unprotected CA (Fig 2). Regression analysis of this relationship predicts that at 18°C, the percent recovery of CMRO₂ = $(-0.86)(\text{CA duration}) + 97$; ($r^2 = 0.73$; $p = 0.0001$). By contrast, systemic oxygen consumption recovered to Pre values in all groups.

Topical cooling of the head during 60 minutes of CA significantly improved recovery of CMRO₂ as compared with 60 minutes of CA without topical cooling. In animals treated with trickle-flow, CMRO₂ fully recovered to Pre values. Figure 3 illustrates the efficacy of these protective measures as demonstrated by percent recovery of CMRO₂. In addition to CMRO₂, CBF and cer DO₂ were also reduced after CA. However, cer a-vO₂ and the cerebral oxygen extraction ratio were unchanged from Pre values in all groups.

Comment

The "Safe" Duration of Circulatory Arrest

Relative to other organs in the body, the brain's metabolic requirement for oxygen is high and its tolerance to ischemia is low. This is the obvious limitation to CA. To achieve "safe" CA, hypothermia is used to reduce, but not eliminate, the cerebral demand for oxygen during the period that oxygen supply is unavailable. Data from this study (see Tables 1, 2) reinforce the fact that in spite of cooling to 18°C, over 30 minutes, cerebral requirements for oxygen persist at a significant level when CA is initiated. Others have documented similar findings. In the laboratory setting, CMRO₂ in dogs at 20°C remained 35% to 40% of normothermic values immediately before CA [5, 6]. Clinically, data from our institution also confirm that CMRO₂ in infants remains significant at the time circulatory arrest is initiated [7].

The true safe interval for hypothermic CA ends at that time when the demand for oxygen is unfulfilled and some degree of ischemia ensues. The present study suggests that a measurable impairment of cerebral metabolic function may occur within minutes of beginning hypothermic CA. As shown in Table 2, recovery of CMRO₂ was significantly reduced after only 15 minutes of CA. However, CBF was unchanged over the same period. There-

fore, impairment of CMRO₂ is likely due to one or both of the following mechanisms: redistribution of blood flow away from oxygen-consuming cells or a primary inability to utilize delivered oxygen. Aoyagi and associates [8] and Hossmann and colleagues [9] have both demonstrated substantial changes in regional cerebral blood flow after hypothermic CA. Perna and co-workers [6] performed continuous measurements of cerebral cortical tissue oxygen tension and observed a rapid depletion of oxygen tension immediately after initiation of CA. Utilization of oxygen by the brain ceased within the first 15 minutes of the arrest period.

The CA-induced metabolic impairment noted at hypothermia continued after rewarming to 37°C and weaning off bypass (see Table 3). At Pre and Post measurements, systemic blood flow was pulsatile, and mean arterial blood pressure and systemic cardiac output did not differ significantly in any group. In control animals, postbypass CMRO₂ recovered fully to baseline values. In animals receiving CA, postbypass CMRO₂, CBF, and cer DO₂ were all lower when compared with Pre values. However, cer a-vO₂ and cer O₂ Extraction were unchanged in these groups, and therefore the impairment of CMRO₂ was not due to limitation of global oxygen delivery.

Contrary to perceptions that CA is physiologically inconsequential until 30 to 45 minutes, this study defined a linear relationship between duration of CA and impairment of cerebral metabolism (see Fig 2). Impairment of cerebral metabolism begins immediately and becomes progressively worse as the duration of circulatory arrest lengthens. A similar relationship was described by Fisk and colleagues [10, 11], who studied neonatal piglets with electroencephalography before, during, and after variable periods of CA at 20°C. Results demonstrated that electroencephalographic activity ceased within seconds of CA and that return of electroencephalographic activity was significantly delayed as compared with several sets of controls. Most importantly, the delay in return of electroencephalographic activity was linearly related to the duration of CA. Histologic specimens obtained 10 days after CPB found consistent lesions in the cerebral cortex of CA animals that were identical to lesions found in control animals subjected to 5 minutes of warm anoxia.

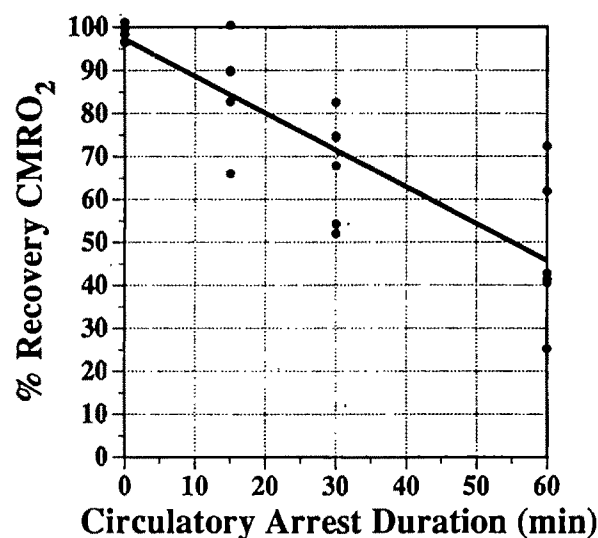
Table 3. Cerebral Metabolic Parameters for Each Experimental Group Before and After Cardiopulmonary Bypass

Group*	CMRO ₂ (mL · 100 g ⁻¹ · min ⁻¹)		CBF (mL · 100 g ⁻¹ · min ⁻¹)		Cer DO ₂ (mL · 100 g ⁻¹ · min ⁻¹)		Cer a-vO ₂ (mL/dL)		Cer O ₂ Extraction Ratio	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Control	1.84 ± 0.05	1.82 ± 0.06	20.8 ± 2.5	20.6 ± 3.0	3.16 ± 0.44	2.78 ± 0.40	9.45 ± 1.19	9.55 ± 1.32	0.63 ± 0.09	0.70 ± 0.08
15'CA	1.79 ± 0.13	1.53 ± 0.14 ^b	19.1 ± 1.7	16.9 ± 1.4	2.85 ± 0.39	2.30 ± 0.15	9.49 ± 0.56	9.39 ± 1.28	0.66 ± 0.08	0.67 ± 0.07
30'CA	1.97 ± 0.09	1.34 ± 0.12 ^{c,d}	30.4 ± 7.9	19.3 ± 3.1	4.42 ± 1.06	2.55 ± 0.45 ^c	8.41 ± 0.35	8.16 ± 0.68	0.52 ± 0.07	0.56 ± 0.06
60'CA	2.10 ± 0.19	1.06 ± 0.12 ^{c,d}	26.0 ± 1.9	13.3 ± 1.9 ^c	4.01 ± 0.39	1.66 ± 0.28 ^c	8.98 ± 0.75	8.23 ± 0.82	0.59 ± 0.06	0.68 ± 0.05
60'CA-TC	1.92 ± 0.16	1.50 ± 0.17 ^{b,c}	26.0 ± 2.2	17.5 ± 2.0 ^c	3.81 ± 0.39	2.06 ± 0.26 ^c	7.59 ± 0.78	8.94 ± 0.90	0.52 ± 0.05	0.75 ± 0.05 ^c
60'TF	1.97 ± 0.18	1.82 ± 0.21 ^b	22.9 ± 2.2	16.9 ± 1.8	3.67 ± 0.31	2.55 ± 0.26	9.03 ± 1.26	10.8 ± 0.58	0.56 ± 0.08	0.71 ± 0.03

* Groups are defined in Figure 1. ^b $p < 0.05$ versus 60'CA-Post by analysis of variance.CBF = cerebral blood flow; Cer a-vO₂ = cerebral arteriovenous oxygen content difference; Cer DO₂ = cerebral oxygen delivery; Cer O₂ Extraction Ratio = CMRO₂/Cer DO₂; CMRO₂ = cerebral metabolic rate of oxygen.^c $p < 0.05$ versus Pre by paired t test.^d $p < 0.05$ versus CTL-Post by analysis of variance.

$$\% \text{ Recovery CMRO}_2 = (-0.86 \times \text{CA Duration}) + 97$$

$$r^2 = 0.73$$

Fig 2. Percent cerebral metabolic rate of oxygen (CMRO₂) recovery versus duration of circulatory arrest: Least-squares regression of percent recovery of cerebral metabolism versus duration of circulatory arrest (CA) demonstrated a linear relationship with $r^2 = 0.73$ ($p = 0.0001$). This relationship is predicted by the formula: %Recovery CMRO₂ = $(-0.86 \times \text{CA duration}) + 97$.

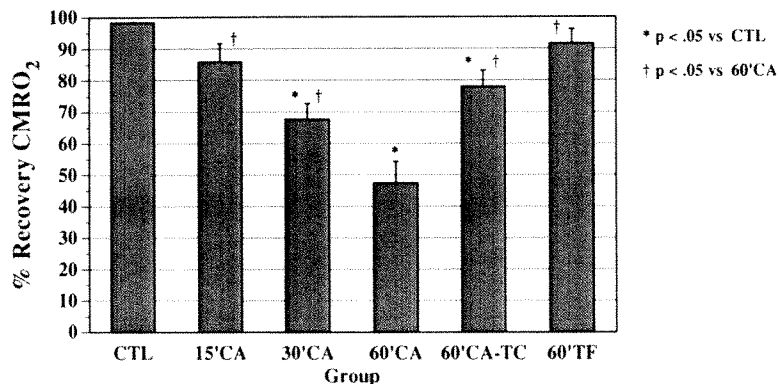
These patterns of responses reflect measurable metabolic and histologic changes that occurred immediately after CA and continued after weaning from bypass. However, correlates between structural injury and functional sequelae are also important. Clinical studies conducted at our institution are consistent with these laboratory findings [7]. In this study of 46 pediatric patients receiving hypothermic CPB, cerebral metabolism and oxygen extraction were significantly reduced during rewarming and after bypass and suggested disordered cerebral metabolism and oxygen utilization after deep hypothermic CA. The results of other clinical studies that included long-term follow-up are mixed [12-14].

Cerebral Protection

Having defined the relationship between CA duration and metabolic impairment, methods of cerebral protection were objectively evaluated. Topical cooling of the head is routinely used at several institutions. In this investigation, topical cooling of the head ameliorated the metabolic impairment of 60 minutes of CA. This benefit was most likely due to further reduction of the cerebral oxygen requirements by cooling the head to an average of 12.6°C, thereby delaying the time to ischemia. Packing the head in ice can be performed without difficulty in the clinical setting, and is recommended for CA. Although regional metabolism of other organs was not measured, systemic oxygen consumption recovered fully after circulatory arrest at 18°C.

Recent data suggest that hypothermia causes changes

Fig 3. Efficacy of protective strategies on percent cerebral metabolic rate of oxygen (CMRO_2) recovery: Topical cooling by packing the head in ice reduced nasopharyngeal temperature to 12.6°C during 60 minutes of circulatory arrest (CA). This intervention demonstrated a clear improvement in recovery of cerebral metabolism as compared with 60 minutes of CA without topical cooling. More dramatically, CMRO_2 recovery was greater than 90% when trickle-flow cardiopulmonary bypass was maintained at 5 to $10 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ at 18°C for 60 minutes. (CTL = control; groups are defined in Figure 1.)



at the cellular level that may enhance tolerance of ischemia [15]. This has led some investigators to explore the use of extreme hypothermia (less than 10°C) to extend the "safe" period of CA to 90 to 180 minutes [16, 17]. Further study will be required to determine the safety of these exceptionally low temperatures.

Continuous, low (trickle) flow also demonstrated efficacy for cerebral protection in this study. With perfusion at 5 to $10 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and 18°C for 60 minutes, cerebral metabolism fully recovered after CPB. This flow rate was chosen to simulate the clinical setting where the minimum sustainable flow from a $\frac{1}{4}$ -inch raceway in a standard roller pump head is 5 to $10 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. Other investigators have also studied various low-flow perfusion strategies. Miyamoto and colleagues [18] recommended an optimal perfusion flow rate of $30 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, whereas Swain and associates [19] maintained high-energy phosphate concentrations with flow rates of $10 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. Others [20] have successfully combined pulsatile blood flow with low-flow perfusion. Studies of regional perfusion during low-flow hypothermic perfusion indicate that all areas of the brain remain perfused [21]. Hypothermic low-flow perfusion combines a reduction of oxygen requirement with continued oxygen delivery and provides superior protection of the brain by minimizing the potential for cerebral ischemia. It is recommended when technically feasible.

This investigation describes a pattern of cerebral metabolic response to varying periods of ischemia at 18°C and provides an objective set of indices that should permit evaluation of new cerebral protective strategies. Clinical studies at our institution have been performed using these measurement techniques and experimental protocols with similar results. Therefore, the animal model used in this study encourages further investigation of specific questions related to cerebral protection with the expectation that the results will be clinically relevant.

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DISCUSSION

DR JULIE A. SWAIN (Las Vegas, NV): Several years ago we also used nuclear magnetic resonance spectroscopy to look at low flows. I wonder why you chose 5 to 10 mL · kg⁻¹ · min⁻¹. We showed that 10 mL · kg⁻¹ · min⁻¹ was great and that 5 mL · kg⁻¹ · min⁻¹ was minimally protective. Is there not some work from your institution to suggest exactly what the lower limit of flow should be?

DR MAULT: We are very aware of your significant contributions to this field. Our flow rate of 5 to 10 mL · kg⁻¹ · min⁻¹ was selected as the minimum amount of flow that could be used during this period to facilitate a clear operative field and yet at the same time provide cerebral protection. We recognize that your data using nuclear magnetic resonance showed a less than optimal response with 5 mL · kg⁻¹ · min⁻¹. However, we think that there may be some benefit during 60 minutes of circulatory arrest.

DR SWAIN: My other question is on your venous oxygen saturation data. Can we assume that one might be able to monitor cerebral venous oxygen saturation, because that is relatively easy to do versus xenon or microspheres, to see adequacy of oxygen delivery and how we might affect delivery in the postoperative period?

DR MAULT: Measurement of venous saturation is a reliable reflection of oxygen consumption and delivery relationships; however, there is a contrast between these data and the data that were just presented in that we saw no change in the arterio-venous oxygen extraction ratio. What actually happened in this series of data is that the cerebral blood flow also went down in parallel with the cerebral metabolic rate, and therefore the extraction ratio did not change. In that situation the sagittal sinus saturations would not reflect the impairment.

DR JOHN C. ALEXANDER, JR (Evanston, IL): I enjoyed your report. I would like to make a comment and then offer a suggestion. The models that we have seen today are interesting. They mimic the pediatric group of patients who are treated with hypothermic arrest in that the aorta is closed. If the aorta is closed you can use the antegrade "trickle" technique that Paul Ebert popularized. I think the information you have shown is really quite good to document its importance and usefulness.

In the adult patient, when we are faced with aortic reconstructions, we almost always are working on an open aorta. There are some interesting technical differences when the aorta is open in that the potential for air embolization and debris embolization is present. We have used the trickle technique but have used it differently in the adult setting. We pump backward into the right atrium at the trickle flow rate and are able to see blood coming retrograde out of the head vessels. We think we accomplish the same thing in a practical sense. We have done this in 10 patients

and have not had any neurologic problems in some extended periods of aortic reconstruction. I would suggest you try this model with the aorta open and use the reverse trickle technique. Somehow the blood finds its way back through the brain. We have measured the oxygen content as blood comes out of the head vessels and it is really very low compared with the oxygen content of blood going into the right atrium. This technique also provides excellent myocardial protection; it gives you retrograde cardioplegia, if you will.

DR MAULT: Thank you very much. I am quite excited about that suggestion. In fact, in the laboratory at this time we are currently performing studies to follow up on what the mechanism of this protection might be, and I agree with you wholeheartedly that some minimum perfusion of the brain may be simply clearing the metabolic wastes, the acids, whatever, that may be building up during the circulatory arrest period, and that accomplishing this by whatever means may be protective.

DR ALEXANDER: I think there are a couple of other things you can say about this technique. First, it will maintain the hypothermic temperature of the brain better than you can do with topical cooling, and second, it prevents air locks from getting into the brain. If you watch what happens when you open the aorta and still have your venous reservoir open, you see blood followed by air sucked through the venous cannula. I think you create air locks in the brain. The first report that was presented showed a vulnerable period that becomes very important. It is during that period that the air locked spots in the brain do not get perfused and are damaged.

DR RANDALL B. GRIEPP (New York, NY): I have one comment, and then I should like to ask you to respond to two discrepancies between your studies with the piglet model and ours with the dog. The comment is that I am delighted to see experimental data supporting the fact that topical cooling of the head is important. I think that in many cases of neonatal surgery and aneurysm surgery the head has not been packed in ice during the period of circulatory arrest, and unnecessary cerebral damage has resulted.

The two discrepancies between your studies and ours are, first, that after 45 or 90 minutes of circulatory arrest, we do not see any significant fall in cerebral metabolic rate for oxygen in the postbypass period as compared with the normothermic control. We do, however, see remarkably reduced cerebral blood flow with maintenance of normal CMRO₂ by increased oxygen extraction. As I understand it in your animals there is almost always some degree of reduction in cerebral metabolic rate for oxygen in the early postbypass period. Second, perhaps you could comment on the difference in the basal cerebral metabolic rate for oxygen. In our weanling puppies, using microspheres to measure blood flow, cerebral metabolic rates for oxygen vary between

3.5 and 5 mL/100 g of brain per minute in the normothermic anesthetized state. In your piglets the corresponding figure, as I understand, it is approximately 1.5 to 2 mL/100 g of brain tissue per minute.

DR MAULT: Thank you very much. There is definitely some disparity between these two models, however, we are measuring these parameters at two different time points, and it very well

may be that CMRO₂ recovered fully if this is measured 2 hours after bypass. In our study, post measurements were taken at 30 minutes immediately after stabilization off bypass, and that may be a factor. There is also a species difference that certainly has to be considered, and at the same time, within our species of piglet model, these CMRO₂ values and the cerebral blood flows are both consistent with piglet studies of this type that have been conducted by Fisk and others over the last 20 years.

Notice From the American Board of Thoracic Surgery

The part I (written) examination will be held at the Hilton Executive Conference Center, Dallas Fort Worth Airport, Dallas, TX, on February 13, 1994. The closing date for registration is August 1, 1993.

To be admissible for the part II (oral) examination, a candidate must have successfully completed the part I (written) examination.

A candidate applying for admission to the certifying examination must fulfill all the requirements of the board in force at the time the application is received.

Please address all communications to the American Board of Thoracic Surgery, One Rotary Center, Suite 803, Evanston, IL 60201.

Improved Multiorgan Function After Prolonged Univentricular Support

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Eleven cardiac transplant candidates (all male; mean age, 43.3 years) with multiorgan (hepatic, pulmonary, and/or renal) dysfunction were sustained for prolonged periods (>30 days) with the HeartMate (Thermo Cardiosystems, Inc, Woburn, MA) left ventricular assist device. We evaluated the effect of extended support on end-organ recovery and on the ultimate outcome of cardiac transplantation. In addition to cardiac failure, 9 patients had hepatic dysfunction, 8 had pulmonary dysfunction, and 6 had renal dysfunction (4 of whom required hemodialysis before left ventricular assist device support). Mean duration of support was 115 days (range, 31 to 233 days). All patients underwent successful transplantation; 10 of these patients survived a mean of 24 months. One patient, who had required hemodialysis and ventilatory support during and after support, experienced progressive multiorgan failure and died 7 weeks after transplan-

tation. Two late deaths after transplantation were unrelated to the device. Overall, patients experienced improvement in cardiac functional class status, and most participated in cardiac rehabilitation programs before transplantation. During left ventricular assist device support, hepatic function returned to normal in 8 patients, pulmonary function recovered in 7, and renal function returned to normal in 4. One patient who required hemodialysis underwent renal transplantation after cardiac transplantation and had complete recovery of renal function. In the current era of donor shortages, gravely ill patients can benefit from a strategy of prolonged left ventricular assist device support. This strategy has proved safe, has allowed for reversal of multiorgan dysfunction, and has produced healthier transplant candidates.

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A variety of circulatory support devices have proved effective for the temporary support of patients awaiting cardiac transplantation [1-3]. The benefits of circulatory support in patients being bridged to transplantation, however, are often limited by the increased risks from device-related complications [4]. Consequently, many centers favor shorter periods of mechanical circulatory assistance, and patients undergo transplantation as soon as possible [5, 6]. Some of these patients experience multiorgan dysfunction either before or during the time of support and are not necessarily optimal transplant candidates [2, 3, 5]. Unfortunately, many such patients are excluded from the benefits of cardiac transplantation on the basis of impaired end-organ function, despite an overall survival rate that is comparable with that in transplant recipients who did not require any form of mechanical assistance before the operation [2, 6, 7].

Extended mechanical support has been shown to result in improved end-organ function and to create a healthier recipient candidate [3, 8, 9]. In clinical studies that have been ongoing at our institution for more than 5 years, the HeartMate (Thermo Cardiosystems, Inc, Woburn, MA) left ventricular assist device (LVAD) has been used suc-

cessfully during periods of prolonged support and has proved both safe and reliable [10, 11]. Evidence from this experience suggests that prolonged support may be beneficial because of the significant delay between improvement in post-LVAD hemodynamic function and subsequent end-organ recovery. To assess the effect of extended support in potential recipients with multiorgan dysfunction, we evaluated 11 patients who required prolonged support (>30 days) before cardiac transplantation and determined its impact on end-organ recovery and on the ultimate outcome of cardiac transplantation.

Patients and Methods

Of the 328 patients who have undergone cardiac transplantation at the Texas Heart Institute since 1986, 18 (5.5%) required an LVAD as a bridge to transplantation. Eleven of these patients (3.3%) were supported for more than 30 days before a suitable donor heart was obtained. To determine the effects of prolonged LVAD support on end-organ function, we examined indices of hepatic, pulmonary, and renal function in these 11 patients before and during LVAD assistance.

All of the patients were male (mean age, 43.3 years; range, 22 to 55 years). Each patient was receiving maximal pharmacologic support with various combinations of vasoactive medications (ie, dopamine, dobutamine, amrinone, epinephrine, or norepinephrine) at the time of

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LVAD placement. Eight of the patients were treated with the HeartMate after intraaortic balloon pump therapy, and the remaining 3 patients required LVAD placement on an urgent basis, before treatment with the intraaortic balloon pump was attempted. The indication for cardiac transplantation was either ischemic (5 patients) or idiopathic (6 patients) cardiomyopathy. Only one patient in this series had undergone a previous cardiac operation.

Gated nuclear scan studies were done in all patients before LVAD insertion. The average left ventricular ejection fraction was 0.17 (range, 0.08 to 0.26), and the average right ventricular ejection fraction was 0.21 (range, 0.12 to 0.27).

Implantation of the HeartMate was restricted to patients who had been approved for cardiac transplantation and who met specific treatment criteria: inotropic support, intraaortic balloon pump support (if possible), and left atrial pressure or pulmonary capillary wedge pressure greater than 20 mm Hg with systolic blood pressure less than 80 mm Hg or cardiac index less than $2.0 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$. Patients who met the criteria and who were considered to have reversible hepatic, renal, or pulmonary dysfunction were considered acceptable for undergoing prolonged support.

Hepatic dysfunction was defined as a serum total bilirubin concentration greater than $34.2 \mu\text{mol/L}$ (2.0 mg/dL) or a serum glutamic-oxaloacetic transaminase concentration greater than 500 IU/L. Renal dysfunction was defined as an increase in serum creatinine level to greater than $176.8 \mu\text{mol/L}$ (2.0 mg/dL) or an increase in blood urea nitrogen level to greater than 14.3 mmol/L (40 mg/dL), with recent onset of severe oliguria or anuria despite diuretic administration. Our definition of renal dysfunction also included the need for hemodialysis as a result of cardiac failure before LVAD insertion or at any time after cardiac transplantation. A patient was considered to have pulmonary dysfunction when mechanical ventilatory support was needed before operative intervention, when radiographic evidence of severe pulmonary edema was present, or when major respiratory limitations to even mild exercise were present.

Improvement in cardiovascular function was assessed by comparing hemodynamic indices just before LVAD insertion and after 72 hours of LVAD support. Improvement in hepatic function was measured by comparing total bilirubin concentration and serum glutamic-oxaloacetic transaminase level, as well as other biochemical measures of hepatic function (serum glutamic-pyruvic transaminase level and prothrombin time), before instituting support and at the time of transplantation. Renal function was similarly evaluated by comparing serum markers (creatinine and blood urea nitrogen levels), the presence of oliguria ($<0.5 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$), or the requirement for hemodialysis before LVAD insertion and at the time of transplantation. Pulmonary function was assessed by comparing serial chest radiographs obtained before and after LVAD implantation, the need for prolonged mechanical ventilation, and the recovery of respiratory function in response to exercise.

All patients had been approved by the St. Luke's

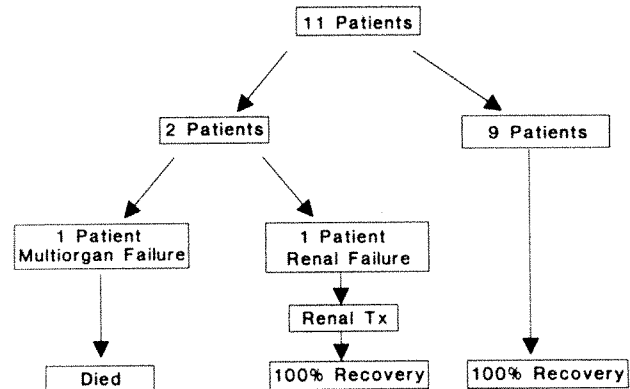


Fig 1. Summary of experience in 11 patients with multiorgan dysfunction who required prolonged (>30 days) left ventricular assist device support as a bridge to transplantation (Tx).

Episcopal Hospital Medical Review Board for cardiac transplantation and were on the active transplant waiting list before LVAD insertion. Informed consent was obtained before LVAD insertion, and all other Institutional Review Board guidelines were followed.

Device Description

The HeartMate LVAD is a pneumatically actuated, abdominally positioned LVAD that consists of a pulsatile pusher-plate blood pump within a rigid titanium housing [10]. All blood-contacting surfaces, except the 25-mm porcine xenograft valves within the inlet and outlet conduits, are textured with either sintered-titanium microspheres or integrally textured polyurethane [12], and these surfaces promote the formation of a biologic lining. The device has a maximum stroke volume of 85 mL and is capable of providing blood flows up to 10 L/min. The techniques for device implantation have been described [13].

Postoperative Management

To reduce the incidence of infections after LVAD implantation, oximetric pulmonary artery catheters and chest tubes were usually removed within 72 hours of the implant operation. Dextran was administered in the early postoperative period and was converted to low-dose aspirin and dipyridamole when the patient resumed oral intake. Early after operation, patients were encouraged to become mobile, and they usually began a cardiac rehabilitation program (stationary bicycling, walking, and treadmill exercise) by the second week after implantation.

Results

All 11 patients survived LVAD implantation and underwent cardiac transplantation. Mean survival in 10 of the patients was 24 months (range, 49 days to 44 months) (Fig 1). The mean duration of LVAD support was 115 days (range, 31 to 233 days). All but 1 patient received orthotopic cardiac transplants; heterotopic cardiac transplantation was performed in the first patient because of elevated pulmonary vascular resistance.

Table 1. Effects of Prolonged (1,269 days) Left Ventricular Support on End-Organ Function

Functional Index	Mean Level Before Implantation (range)	Mean Level at Explantation (range)
Cardiovascular		
Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	1.83 (1.3-2.78)	3.43 (2.2-5.1)
Pulmonary artery pressure (mm Hg)	34.1 (18-50)	27.6 (16-39)
Pulmonary capillary wedge pressure (mm Hg)	26.0 (7-40)	11.1 (5-20)
Central venous pressure (mm Hg)	14.9 (8-25)	12.4 (6-21)
Hepatic		
Total bilirubin (mg/dL)	4.4 (1.5-10.9)	1.6 (0.4-10.5)
SGOT (mg/dL)	1,233 (32-9,549)	52.3 (22-179)
SGPT (mg/dL)	756 (17-7,345)	70.7 (17-311)
Prothrombin time (s)	13.8 (11.5-18.5)	12.0 (11.0-14.0)
Renal		
Blood urea nitrogen (mg/dL)	59.3 (17-132)	29.3 (13-90)
Serum creatinine (mg/dL)	3.1 (1.1-9.3)	1.5 (0.7-1.7)

SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase.

All 11 patients were in New York Heart Association functional class IV before LVAD implantation despite aggressive medical management. In addition to end-stage heart failure, each patient was experiencing impaired function of at least one other organ before LVAD insertion: 5 patients had evidence of impaired function of three other organs, 3 patients had impaired function of two other organs, and 3 patients had impaired function of one other organ. Altogether, 9 patients had hepatic dysfunction, 8 had pulmonary dysfunction, and 6 had renal dysfunction.

One patient, the first in this series to undergo treatment with the HeartMate, died as a result of systemic candidiasis and cytomegalovirus infection 7 weeks after cardiac transplantation. Hepatic, renal, and pulmonary dysfunction did not recover during LVAD support, and progressive multiorgan failure occurred despite aggressive systemic antibacterial and antifungal therapy. Postmortem examination revealed cirrhosis, in addition to systemic candidiasis and multiorgan failure. Two late deaths occurred: 1 patient died suddenly 34 months after transplantation, the suspected cause being noncompliance with the immunosuppressive regimen, and the other patient died of severe coronary atherosclerosis 29 months after transplantation.

Cardiovascular Function

All hemodynamic indices improved within 24 hours of LVAD insertion. Indices of cardiac function were documented after 72 hours of LVAD support and then compared with those obtained before support was initiated (Table 1). In each patient, a striking improvement was noted in the mean cardiac index (Fig 2), mean pulmonary artery pressure, and pulmonary capillary wedge pressure. The mean central venous pressure was slightly reduced during support. After 30 days of mechanical circulatory support, the cardiac status of all patients had improved: 8 patients were in functional class I, and 3 patients, including the first one in this series, were in functional class II.

Hepatic Function

Nine patients had hepatic dysfunction before LVAD support, and hepatic function had returned to normal in 8 (89%) by the time of LVAD removal. Improvement was reflected by markedly decreased bilirubin (total and direct) levels (Fig 3A), as well as serum glutamic-oxaloacetic and glutamic-pyruvic transaminase levels (Fig 3B). The only patient who did not recover normal hepatic function was the one who died of multiorgan failure in addition to chronic liver cirrhosis. Overall, the biochemical indices representing hepatic function in 10 patients showed marked improvement with prolonged support (see Table 1).

Pulmonary Function

Pulmonary function recovered in 7 of 8 patients who had required mechanical ventilation before LVAD insertion.

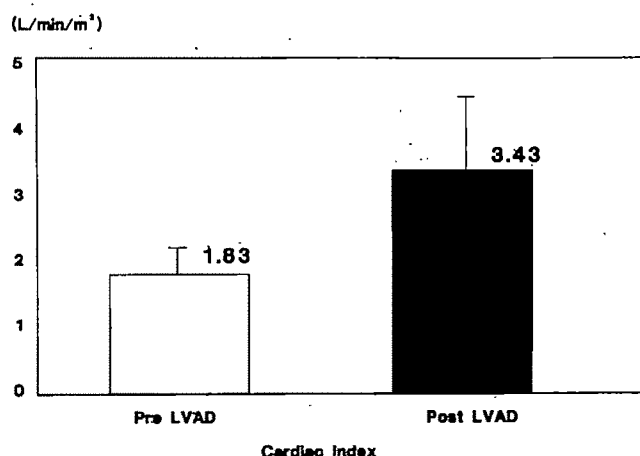
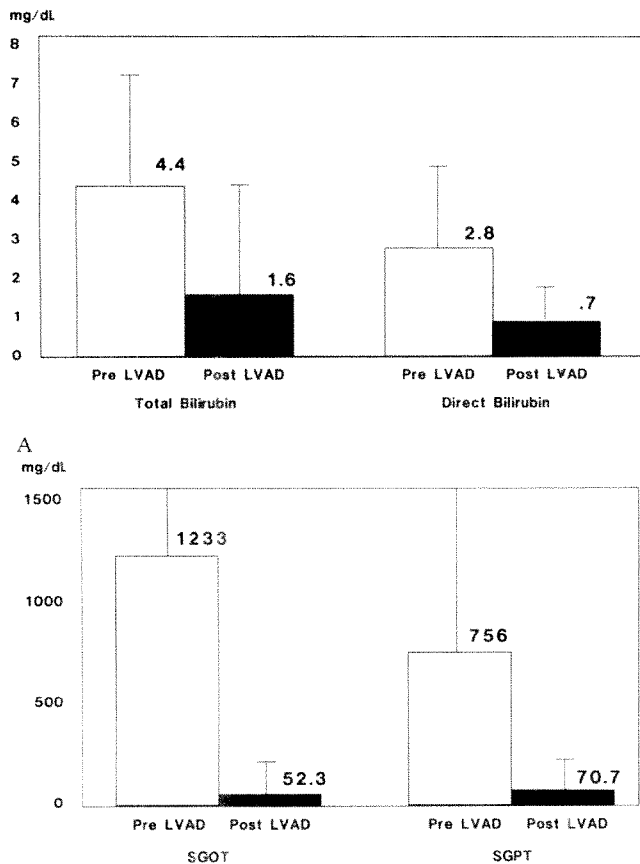


Fig 2. Improvement in cardiovascular function, as evidenced by comparison of cardiac index measurements obtained just before left ventricular assist device (LVAD) implantation and 72 hours after initiation of support.

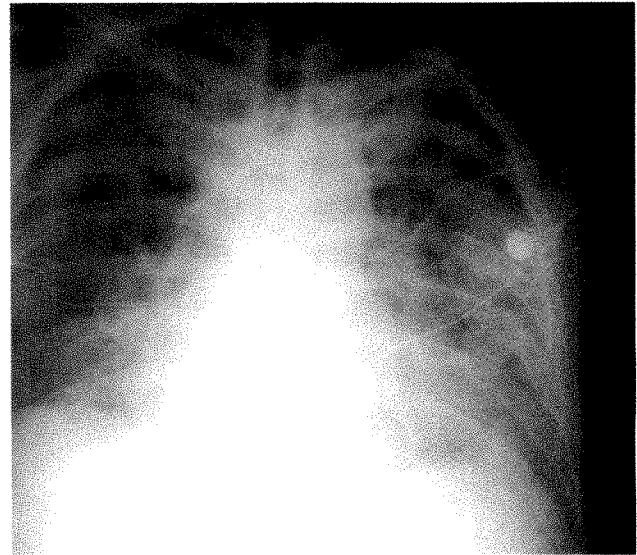


B

Fig 3. Improvement in hepatic function, as evidenced by total and direct bilirubin levels (A) and by serum transaminase levels (B). Measurements were obtained just before left ventricular assist device (LVAD) implantation, and just before LVAD explantation. (SGOT = serum glutamic-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase)

The 7 patients who experienced pulmonary improvement were easily weaned from mechanical ventilation after LVAD implantation. The average time between LVAD implantation and the withdrawal of ventilatory support in 10 of the 11 patients was 4.3 days (range, 1 to 20 days). Five patients were extubated within 48 hours of LVAD insertion, and 3 patients were extubated between 72 and 96 hours; 2 patients required prolonged ventilatory support (10 and 20 days after implantation). The remaining patient, the first patient in this series to undergo treatment, was briefly extubated on several occasions after LVAD implantation and after cardiac transplantation, but each time he required reintubation because of deteriorating mental status and progressive multiorgan failure.

Signs of pulmonary edema were apparent in 6 of the 11 patients before LVAD insertion (Fig 4A). Despite the rapid clinical improvement in respiratory function that allowed early withdrawal of mechanical ventilation, all 6 patients had radiographic evidence of pulmonary edema that persisted for several weeks. Complete resolution of pulmonary edema in all of these patients was seen radiographically within 4 weeks of initiating LVAD support (Fig 4B).



A



B

Fig 4. Improvement in pulmonary function, as evidenced by a representative chest radiographic series. The first chest radiograph was obtained just before left ventricular assist device implantation (A), and the second was obtained just before left ventricular assist device explantation (B).

Before undergoing mechanical support, all 11 patients were confined to bed because of severe dyspnea. By the end of the second week after LVAD insertion, 6 were walking independently, and by 4 weeks, 9 were participating in vigorous cardiac rehabilitation programs.

Renal Function

Four of the 6 patients who had renal dysfunction before LVAD implantation had undergone prior hemodialysis (see Table 1). Three additional patients in whom signs of impending renal dysfunction were present (severe oliguria or anuria) underwent urgent LVAD insertion before serious elevation in blood urea nitrogen or serum creati-

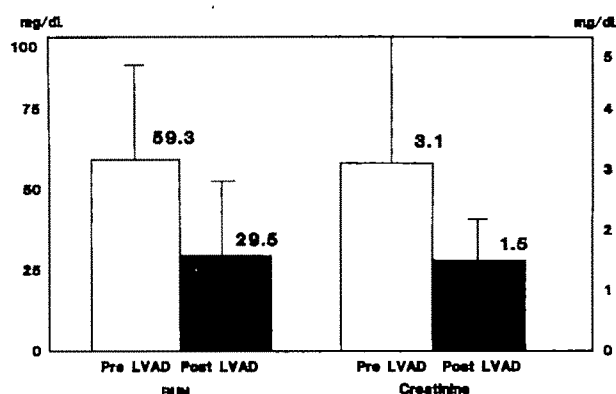


Fig 5. Improvement in renal function, as evidenced by blood urea nitrogen (BUN) and serum creatinine levels. Measurements were obtained just before left ventricular assist device (LVAD) implantation and just before LVAD explantation.

nine levels occurred. After extended LVAD support, all 11 patients exhibited a decline in azotemia, although two remained dependent on hemodialysis. Altogether, the mean blood urea nitrogen level decreased to 10.5 mmol/L (29.5 mg/dL) (range, 4.6 to 32.1 mmol/L [13 to 90 mg/dL]), and the mean serum creatinine level dropped to 132.6 μ mol/L (1.5 mg/dL) (range, 61.9 to 203.3 μ mol/L [0.7 to 2.3 mg/dL]) (Fig 5). When the 2 patients who continued to require hemodialysis were excluded from this analysis, however, the mean blood urea nitrogen and serum creatinine levels after extended LVAD support were even lower, at 6.7 mmol/L (18.9 mg/dL) and 106.1 μ mol/L (1.2 mg/dL), respectively.

In addition to being azotemic, 9 patients were oliguric before LVAD support, 7 of whom had severely diminished urinary outputs. After prolonged LVAD support, urinary outputs returned to normal in 8 patients, including 3 of the 4 patients who needed hemodialysis before LVAD support was initiated. Two of the 3 patients recovered normal renal function with prolonged mechanical support, and hemodialysis was discontinued.

Of the 2 patients who remained dependent on hemodialysis despite prolonged mechanical support, 1 underwent cardiac transplantation, followed by renal transplantation. After renal transplantation, the patient had complete recovery of renal function. The other patient (again, the first patient in this series to undergo treatment) remained on hemodialysis until the time of his death.

Comment

Although cardiac transplantation is now an accepted therapeutic option for the treatment of end-stage heart disease, the scarcity of suitable donor organs suggests that many potential recipients may require some form of mechanical circulatory support before transplantation [3, 4]. Indeed, of the 16,687 patients listed in the International Registry for Heart Transplantation who had received primary cardiac allografts worldwide through January 1, 1991, 363 (2%) had been bridged to transplantation

with either a ventricular assist device or a total artificial heart [6, 14]. The need for pretransplantation circulatory assistance within the United States may be even higher, ranging between 13% and 29% at some centers [1, 7]. As the long-term survival rates for patients undergoing bridged transplant procedures are beginning to approach that of patients undergoing traditional cardiac transplant procedures, a strategy combining mechanical support with cardiac transplantation appears to be justified [6, 7, 9, 15-18].

The primary emphasis in many bridge-to-transplantation programs has been to support device-dependent patients until the first donor organ becomes available [2, 3, 6, 8]. Unfortunately, many heart transplant candidates who are bridged to transplantation have development of multiorgan dysfunction that can limit, or even preclude, successful cardiac transplantation [1, 2, 4]. Early transplantation for these gravely ill patients may not be optimal, because end-organ recovery often lags substantially behind any improvement noted in hemodynamic function after LVAD placement [11]. Although a few centers [3, 8, 9] have noted improvement in end-organ function with longer periods of support, there have been no clinical trials justifying the selective use of long-term support for patients with multiorgan dysfunction.

In the past, the complications of stroke, thromboembolism, and bleeding associated with mechanical circulatory assist devices limited the ability to provide long-term support and to effect improved multiorgan function. The HeartMate not only provides adequate systemic circulation, but also minimizes the risk of thromboembolic complications through the use of textured blood-contacting surfaces, which promote deposition of a stable, biologic lining [11]. Only 1 patient, who was treated at another institution, has experienced a thromboembolic complication [19], which was attributed to a mechanical valve in the native heart, and these results have been achieved despite minimal anticoagulation with aspirin and dipyridamole.

In addition to having reduced thrombogenicity, patients treated with the HeartMate have remained remarkably free from serious infectious complications. Other prosthetic devices that are positioned orthotopically, such as total artificial hearts, do not fill the pericardium, leaving room for potential mediastinal infections. We believe that placing the pump extrathoracically has helped to lower the incidence of infectious complications and to eliminate the potential for mediastinal infections. After abdominal placement, a tissue capsule forms around the pump, similar to the capsule that forms around a pacemaker. The only infections noted in this series occurred at the drive line site, and these responded to local wound care and short-term antibiotic therapy.

Our study demonstrates that prolonged LVAD support in patients bridged to cardiac transplantation can improve organ function if support is initiated before the onset of irreversible organ failure. The 11 patients in the current study had a total of 23 impaired organ systems before LVAD insertion, and function improved in all but four organ systems, three of which were in the first patient in

the series (who died of progressive multiorgan failure). The remaining patient had impaired renal function, but this did not prohibit successful LVAD support or cardiac transplantation. This patient, in fact, underwent uncomplicated renal transplantation approximately 2 months after cardiac transplantation. Although he subsequently died of progressive cardiac allograft atherosclerosis, the remainder of his posttransplantation course was unremarkable.

All 11 patients regained normal hemodynamic function after implantation of the HeartMate, with most experiencing an improvement to functional class I status. The improvement in hemodynamic indices occurred almost immediately after LVAD insertion, and within 2 weeks, the majority of patients were actively engaged in cardiac rehabilitation programs. Recovery of normal end-organ function, however, appears to be slower, and several weeks may pass before functional indices normalize.

Hepatic function improved in all but 1 patient after LVAD support was initiated. Unfortunately, the mechanisms responsible for the improvement in hepatic function remain elusive [20-22]. Because passive venous congestion and hepatic arterial hypoperfusion both appear to contribute to ischemic liver injury [23, 24], it appears that in the absence of elevated pulmonary vascular resistance, left ventricular assistance can adequately provide effective relief of right heart congestion, as well as improve hepatic arterial perfusion [25, 26]. Whether relief of venous congestion or improvement in arterial perfusion was more important cannot be ascertained in this small series.

In contrast to others [2], we have not excluded patients in renal failure from the benefits of mechanical circulatory support or cardiac transplantation. Our current results indicate that impaired renal function does not necessarily affect the interval of LVAD support or the outcome of cardiac transplantation. Reversal of azotemia and oliguria can be expected if support is initiated early and if support is able to be maintained long term [9]. Moreover, even patients who fail to recover renal function despite long-term LVAD support can safely undergo chronic dialysis and can ultimately undergo transplantation.

Despite the delayed clearance of pulmonary edema on chest radiographs, pulmonary function appears to improve early after institution of LVAD support. In the majority of patients in this series, rapid withdrawal of mechanical ventilation was possible, and progressive improvement in exercise tolerance occurred. The response of pulmonary function to LVAD support under conditions of preexisting disease, such as chronic obstructive disease, reactive airway disease, or previous pulmonary resection, may be less favorable. Nonetheless, the rapid improvement in pulmonary function with prolonged LVAD support in 8 of 11 patients who required mechanical ventilation preoperatively strongly supports the concept of univentricular support in patients with pulmonary dysfunction caused by severe heart failure.

Despite extended LVAD support, the first patient in this series died of multiorgan failure as a result of opportunistic infection in the posttransplantation period. Failure to recover hepatic, renal, and pulmonary function, the

inability to resolve persistent systemic fungal infections, and, ultimately, the progression to fulminant multiorgan failure strongly implied that the onset of irreversible organ failure had already occurred by the time of LVAD implantation. This was confirmed by postmortem examination, which revealed cirrhosis, in addition to progressive multiorgan failure. Our subsequent practice has been to assess serious preoperative hepatic dysfunction with transvenous liver biopsy [27]. Histopathologic evidence of fibrotic cirrhosis in biopsy specimens is now regarded as a contraindication to LVAD support and cardiac transplantation.

In conclusion, for patients with end-organ dysfunction that is refractory to maximal medical therapy and intraaortic balloon pump support, intervention with LVAD support can lead to the recovery of normal function. True recovery may, in fact, require prolonged periods of mechanical circulatory support, and this technology is currently available. The restoration of health granted with such support clearly improves one's chances of a smooth posttransplantation course. We have found that prolonged univentricular support is achievable and safe and that it has real efficacy in promoting the successful use of a donor heart in this era of donor organ shortages.

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DISCUSSION

DR J. ALEX HALLER, JR (Baltimore, MD): Dr Burnett, one of the fascinating things about your report is that you are focusing on end organs that can be studied, but the main cause of death in patients with multiple organ failure is sepsis. Did you look at blood cultures during this period? The dramatic thing to me is that you did not have more problems with infection in this group of patients, only 1 I believe you said, who ultimately died of overwhelming infection. Were there decreases in the number of patients with bacteremias, because it is the gut with its translocation that seems to be the main cause of death in this group of patients, and yet that seemed to be reversed with the use of the LVAD.

DR BURNETT: Although the reduced incidence of sepsis in our study group involves many factors, we believe that initiating circulatory support early and maintaining it until end-organ function improves are the main reasons. Using mechanical assistance before irreversible end-organ damage occurs cannot be overemphasized, as evidenced by our previous study in which transplant candidates who had chronic nutritional depletion and end-organ failure underwent early treatment with the HeartMate LVAD. Prolonged support improved visceral protein status, restored serum albumin levels and transferrin levels, and normalized body fat distribution. In addition, use of the HeartMate allowed early resumption of oral food intake and, thus, a return to normal gut function. Consequently, bacterial translocation through attenuated intestinal mucosal barriers is reduced, and, as a result, systemic sepsis may be prevented.

In contrast, the 1 patient who died as a result of sepsis and who was the first to undergo treatment had support initiated late in his course, after end-organ failure was firmly established.

Finally, when LVAD support is initiated early, we have found that virtually all patients with reversible organ dysfunction will return to New York Heart Association class I status, which greatly improves their ability to withstand transplantation.

DR ROBERT A. ALBUS (Fairfax, VA): I wonder if you could comment on the current status of your totally implantable device that you have in. I think it is still functioning now, right?

DR BURNETT: The patient you refer to is a 33-year-old man with severe idiopathic cardiomyopathy who had the electrically actuated LVAD implanted in September 1991. He has been supported by the device for 8½ weeks and has already returned to New York Heart Association class I status. The patient, who carries an 8-hour battery pack in a shoulder harness, is walking and exercising, and he is in better condition now than he had been during the previous 2 years.

The main components of the pneumatic- and electric-powered LVADs are the same, except that a 14F compliance vent and an electric cable have been added to the latter device. Thus, we anticipate that our clinical results with the electric pump will also be positive. Our experience with the pneumatic device and the successful conversion to electrical actuation has excited us in that we may have a model prototype for future permanent implantation.

Component Analysis of Bilateral Anterior Cardiomyoplasty

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This experiment was designed to analyze the mechanism of ventricular augmentation generated with bilateral anterior cardiomyoplasty by comparing it in an acute setting with its components, the left anterior cardiomyoplasty and the right anterior cardiomyoplasty. Hemodynamic variables were measured in 8 dogs before and after each flap was positioned around the heart. Stimulation was achieved by R-wave synchronous latissimus burst pacing at a ratio of 1:4, an amplitude of 5 V, a frequency of 33 Hz, and a duration of 30% of the R-R interval. Hemodynamic changes were again recorded during latissimus stimulation. Construction of the bilateral anterior wrap (static cardiomyoplasty) caused some depression of baseline hemodynamic function, which was greater than that caused by either the static right or

left anterior cardiomyoplasty. With stimulation of the muscles (dynamic cardiomyoplasty), the bilateral wrap caused significant biventricular augmentation. Evaluation of the components of the bilateral wrap demonstrated that dynamic right anterior cardiomyoplasty also provided significant biventricular augmentation, but the dynamic left anterior cardiomyoplasty augmented only right-sided variables. The mechanism of biventricular compression by the bilateral procedure is due mostly to the right wrap. The right anterior cardiomyoplasty may provide significant biventricular compression for treatment of heart failure, without the complexity associated with bilateral anterior cardiomyoplasty.

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The shortcomings of current therapy for congestive heart failure have made it clear that new approaches to this problem are needed [1, 2]. Dynamic cardiomyoplasty is a procedure in which a pedicled latissimus dorsi muscle is wrapped around the heart and paced in synchrony with systole to improve the function of the failing heart. Traditionally, the left latissimus muscle has been employed for cardiomyoplasty because of its close proximity to the heart. Experimental reports have demonstrated that the left latissimus muscle can produce hemodynamic augmentation of an acutely failed left ventricle [3]. However, similar proof of hemodynamic improvement in an animal model of normal ventricular function has been elusive [4].

Bilateral cardiomyoplasty was conceived as a method for covering both ventricles with skeletal muscle to provide biventricular hemodynamic augmentation [5]. Experimental studies have shown significant augmentation of normal [6] and depressed [7] ventricular function with this form of cardiomyoplasty. This experiment was designed to analyze the mechanism of improved biventricular augmentation of a bilateral anterior cardiomyoplasty (BAC). The hemodynamics of BAC in an acute setting were compared with those of its component parts, the left

anterior cardiomyoplasty (LAC) and the right anterior cardiomyoplasty (RAC).

Material and Methods

Eight adult mongrel dogs weighing 27 to 31 kg underwent bilateral latissimus dorsi cardiomyoplasty in a two-stage procedure separated by 7 to 10 days. In the first stage, both latissimus dorsi muscles were mobilized from the chest wall to interrupt all sources of blood supply to the muscles except that from the thoracodorsal pedicles. A "vascular delay" period of 7 to 10 days was used before undertaking the next stage of the procedure, which allowed time for the muscles to recover from division of chest wall perforating vessels. A customized bifurcated paraneural bipolar stimulation lead (Fig 1) was secured to each proximal thoracodorsal nerve. The third end of the three-prong lead was attached to the pacing port of a Prometheus cardiomyostimulator (Medtronic, Inc, Minneapolis, MN).

During the second stage of the experiment, the origins of the latissimus dorsi muscles were separated from their fascial attachments. The humeral insertions of the latissimus dorsi muscles were left intact. Each muscle was then transposed into its respective thorax after resection of a 5- to 7-cm portion of the lateral second or third rib. The bilateral incisions were closed, and a median sternotomy was performed.

The animals were instrumented in the following fashion. A flow-directed pulmonary artery catheter and a

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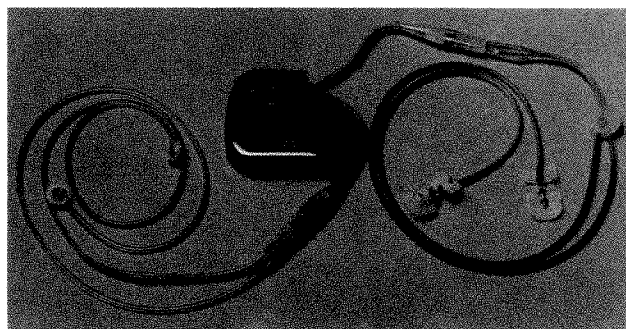


Fig 1. Prometheus cardiomyostimulator with attached screw-in sensing leads (left) and custom-made bifurcated paraneural stimulation leads (right).

Millar transducer-tipped aortic catheter were introduced from the femoral vessels. After the pericardium was opened, saline-filled plastic catheters were placed directly into the right ventricle, left ventricle, and left atrium and connected to pressure transducers. A 16-mm ultrasonic flowprobe (Transonic Systems, Inc, Ithaca, NY) was placed around the ascending aorta for measurement of aortic flow. All hemodynamic variables were recorded simultaneously by an IBM-AT computer through an analog to digital converter. The data were then analyzed using CODAS and ASYSTANT software (Dataq Instruments, Inc, Akron, OH).

Two epicardial unipolar sensing leads (model 4951, Medtronic) were placed on the anterior wall of the right ventricle. These were connected through a Y-adaptor (model 5866-24, Medtronic) to the sensing port of the Prometheus cardiomyostimulator (see Fig 1).

The BAC consists of two component parts: the RAC and the LAC (Fig 2). Each of these components was applied to the heart in an anterior cardiocostal fashion [8], that is, with the proximal portion of the muscle on the anterior heart and the deep (costal) surface abutting the epicardium. For the creation of an RAC (Fig 3), the lumbodorsal

origin of the right latissimus dorsi muscle was secured to the posterior pericardium at the level of the atrioventricular groove. The proximal muscle flap and its fibers lie on the anterior wall nearly parallel to the long axis of the heart. Construction of the LAC has been previously described [9]. In this type of cardiomyoplasty the fibers of the LAC are parallel to short axis of the heart (perpendicular to the intraventricular septum). The BAC created by placing an LAC on top of the RAC for an encircling "criss-cross" effect on the ventricles.

Baseline hemodynamic measurements were taken before the application of the three cardiomyoplasty wraps to the heart. Latissimus muscles were then retrieved from their respective chest cavities and BAC, LAC, and RAC wraps were performed in each dog in a random order. After each flap was positioned around the heart, a second set of hemodynamic variables was recorded with the muscles in an unstimulated, "static" state.

To prevent muscle fatigue, these nonconditioned latissimus muscles were then burst-paced in synchrony with systole at a ratio of 1 muscle contraction to every 4 heart beats. Cardiomyostimulator-programmed pacing parameters included an amplitude of 5 V, a burst frequency of 33 Hz, a pulse width of 210 microseconds, and a burst duration of 30% of the R-R interval. Hemodynamic measurements were then recorded during "dynamic" cardiomyostimulation.

All animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals," published by the National Institute of Health (NIH publication No. 85-23, revised 1985). All animals were killed after completion of hemodynamic studies.

Results

Each dog served as its own control for statistical analyses. Intraflap hemodynamic analyses of dynamic cardiomyostimulation were done using paired *t* testing with significance interpreted as *p* less than 0.05. Interflap comparisons were performed by repeated-measures analysis of

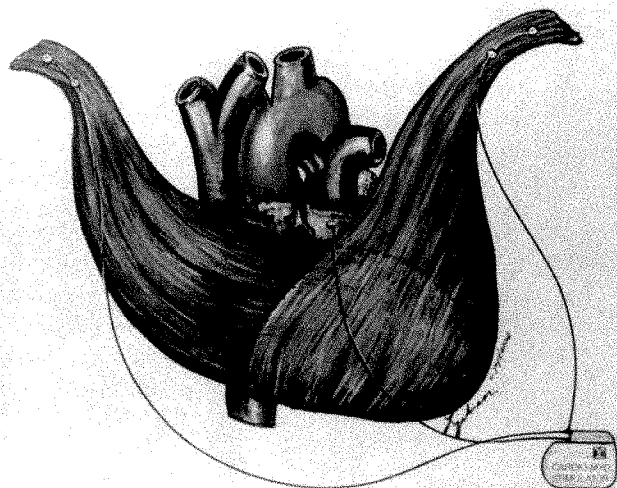
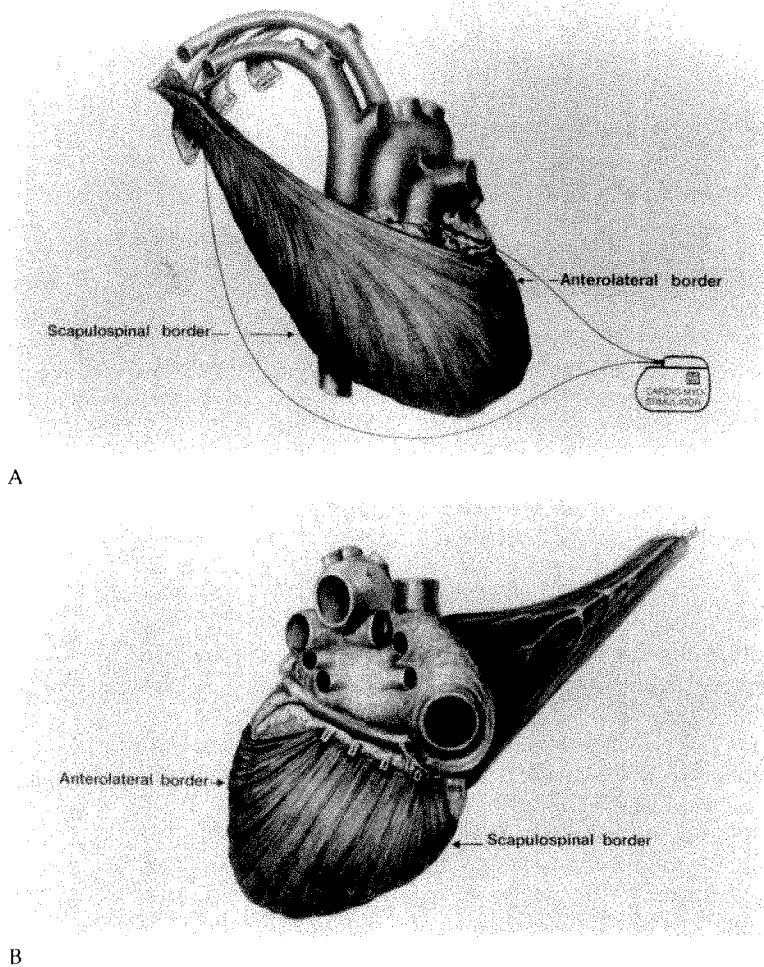


Fig 2. The bilateral anterior cardiomyoplasty is composed of a right anterior and left anterior latissimus flap in a "criss-cross" configuration.

Fig 3. The right anterior cardiomyoplasty sling: (A) anterior view and (B) posterior view. Note the complete biventricular coverage obtained with this flap and parallel positioning of the latissimus fibers to the intraventricular septum throughout.



variance. Significance levels were set at p less than 0.02 with Bonferroni's correction applied.

Baseline Hemodynamics

Baseline hemodynamic variables recorded for each cardiomyoplasty showed no significant differences in right- or left-sided variables through the course of these experi-

ments (Table 1). This indicates that the hemodynamic stability of the native cardiovascular system was maintained over the course of the experiment.

Mean baseline values are shown on all further tables of intraflap comparisons for purposes of simplifying the illustrations. However, statistical comparisons with baseline function were continued in a paired fashion.

Table 1. Baseline Hemodynamics ($n = 8$)

Variable	Bilateral Cardiomyoplasty	Left Cardiomyoplasty	Right Cardiomyoplasty
RV (mm Hg)	32 ± 3	31 ± 2	31 ± 3
RV dP/dt (mm Hg/s)	452 ± 75	423 ± 70	435 ± 80
PA (mm Hg)	26 ± 3	26 ± 2	26 ± 3
LV (mm Hg)	108 ± 6	107 ± 6	104 ± 7
LV dP/dt (mm Hg/s)	$2,086 \pm 169$	$1,996 \pm 119$	$1,966 \pm 200$
Ao P (mm Hg)	98 ± 5	100 ± 4	97 ± 5
Ao flow (L/min)	15.1 ± 1.0	14.7 ± 0.9	14.3 ± 1.1
RA (mm Hg)	7.3 ± 1.3	6.6 ± 1.1	7.4 ± 1.3
LA (mm Hg)	7.9 ± 1.5	8.0 ± 1.9	7.8 ± 1.5

Ao flow = peak aortic flow; Ao P = systolic aortic pressure; LA = left atrial mean pressure; LV = peak left ventricular pressure; LV dP/dt = rate of change of left ventricular pressure; PA = systolic pulmonary artery pressure; RA = right atrial mean pressure; RV = peak right ventricular pressure; RV dP/dt = rate of change of right ventricular pressure.

Table 2. Postwrap Hemodynamics ($n = 8$)

Variable	Baseline	Static Bilateral Cardiomyoplasty	Static Left Cardiomyoplasty	Static Right Cardiomyoplasty
RV (mm Hg)	31 ± 1	28 ± 1	27 ± 3	31 ± 1
RV dP/dt (mm Hg/s)	437 ± 41	206 ± 19 ^a	250 ± 27	235 ± 38
PA (mm Hg)	26 ± 1	23 ± 1	23 ± 2 ^a	27 ± 2
LV (mm Hg)	106 ± 4	78 ± 3 ^{a,b}	89 ± 2 ^a	91 ± 5 ^a
LV dP/dt (mm Hg/s)	2,016 ± 92	1,299 ± 93 ^{a,b}	1,660 ± 124 ^a	1,625 ± 138
Ao P (mm Hg)	98 ± 2	74 ± 3 ^{a,b}	86 ± 3 ^a	84 ± 3 ^a
Ao flow (L/min)	14.7 ± 0.6	8.9 ± 1.0 ^{a,b}	11.0 ± 0.9 ^a	10.3 ± 1.0 ^a
RA (mm Hg)	7.1 ± 0.7	9.3 ± 1.8 ^b	7.6 ± 1.3	9.6 ± 1.6 ^a
LA (mm Hg)	7.9 ± 0.9	9.4 ± 2.0	8.9 ± 1.6	9.3 ± 1.7

^a $p < 0.05$ versus baseline. ^b $p < 0.01$, bilateral cardiomyoplasty versus left cardiomyoplasty or right cardiomyoplasty.

Ao flow = peak aortic flow; Ao P = systolic aortic pressure; LA = left atrial mean pressure; LV = peak left ventricular pressure; LV dP/dt = rate of change of left ventricular pressure; PA = systolic pulmonary artery pressure; RA = right atrial mean pressure; RV = peak right ventricular pressure; RV dP/dt = rate of change of right ventricular pressure.

Static Postwrap Hemodynamics (Unstimulated)

The placement of unstimulated muscle mass around the heart (static cardiomyoplasty) caused some depression of the native baseline hemodynamic ventricular function (Table 2). The static BAC caused significant depression of right ventricular rate of pressure change (dP/dt), left ventricular peak pressure and dP/dt, aortic systolic pressure, and peak aortic flow. The unstimulated LAC effected a decrease in systolic pulmonary artery pressure, peak left ventricular pressure and dP/dt, aortic systolic pressure, and peak flow. Application of the static RAC to the heart depressed the least number of hemodynamic variables. Significant negative alterations were observed in peak left ventricular pressure, systolic aortic pressure, and aortic flow.

Analysis by repeated-measures analysis of variance showed that the static BAC caused more disturbance of normal hemodynamics than either of the unilateral wraps. The changes associated with static RAC or LAC were minor.

Dynamic Cardiomyostimulator Hemodynamics

Hemodynamic results of dynamic cardiomyoplasty in all three groups are shown Table 3.

BILATERAL ANTERIOR CARDIOMYOPLASTY. Stimulation of the BAC produced biventricular compression, which resulted in augmentation of both right- and left-sided variables. Highly significant ($p < 0.01$) increases were seen in peak right ventricular (+60%), left ventricular (+19%), pulmonary artery (+35%), and aortic pressures (+11%). Significant ($p < 0.05$) improvements in right ventricular dP/dt (+16%) and peak aortic flow (+10%) were also seen. The increase in left ventricular dP/dt (+10%) was not statistically significant.

LEFT ANTERIOR CARDIOMYOPLASTY. The stimulated LAC provided significant augmentation of right-sided variables only. Right ventricular pressure (+37%), right ventricular dP/dt (+60%), and pulmonary artery systolic pressures (+22%) were significantly ($p < 0.05$) improved with latis-

Table 3. Stimulated Hemodynamics ($n = 8$)

Variable	Bilateral Anterior Cardiomyoplasty		Left Anterior Cardiomyoplasty		Right Anterior Cardiomyoplasty	
	Static	Dynamic	Static	Dynamic	Static	Dynamic
RV (mm Hg)	28 ± 1	45 ± 3 ^a	27 ± 3	37 ± 3 ^b	31 ± 1	42 ± 3 ^a
RV dP/dt (mm Hg/s)	206 ± 19	549 ± 108 ^b	250 ± 27	401 ± 59 ^b	235 ± 38	492 ± 78 ^b
PA (mm Hg)	23 ± 1	31 ± 2 ^a	23 ± 2	28 ± 3 ^b	27 ± 2	34 ± 3 ^b
LV (mm Hg)	78 ± 3	93 ± 6 ^a	89 ± 2	91 ± 4	91 ± 5	102 ± 6 ^a
LV dP/dt (mm Hg/s)	1,299 ± 93	1,436 ± 156	1,660 ± 124	1,700 ± 176	1,625 ± 138	1,856 ± 193
Ao P (mm Hg)	74 ± 3	82 ± 5 ^a	86 ± 3	86 ± 3	84 ± 3	93 ± 4 ^a
Ao flow (L/min)	8.9 ± 1.0	9.8 ± 1 ^b	11.0 ± 0.9	11.1 ± 0.9	10.3 ± 1.0	11.7 ± 1.1 ^a
RA (mm Hg)	9.3 ± 1.8	11.1 ± 1.3	7.6 ± 1.3	8.0 ± 1.3	9.6 ± 1.6	10.0 ± 1.8
LA (mm Hg)	9.4 ± 2.0	9.9 ± 1.9	8.9 ± 1.6	8.9 ± 1.5	9.3 ± 1.7	9.9 ± 1.9

^a $p < 0.001$, static versus dynamic. ^b $p < 0.05$, static versus dynamic.

Ao flow = peak aortic pressure; Ao P = systolic aortic pressure; LA = left atrial mean pressure; LV = peak left ventricular pressure; LV dP/dt = rate of change of left ventricular pressure; PA = systolic pulmonary artery pressure; RA = right atrial mean pressure; RV = peak right ventricular pressure; RV dP/dt = rate of change of right ventricular pressure.

simus contraction. Although augmentation was seen, the increases in left-sided hemodynamic variables produced by the LAC alone were not great enough to be statistically significant.

RIGHT ANTERIOR CARDIOMYOPLASTY. Synchronized contractions of the RAC produced highly significant changes in both right- and left-sided hemodynamic measurements. Right ventricular pressure was increased 35% over the postwrap baseline ($p < 0.01$), right ventricular dP/dt improved 109% ($p < 0.05$), and systolic pulmonary artery pressures increased 26% ($P < 0.05$). Left ventricular pressure increased by 12% with stimulation, aortic pressure was up 13%, and aortic flow improved an average of 14% ($p < 0.01$ for all).

DATA SUMMARY. The dynamic BAC caused large increases in systolic pressure, but also was associated with significant depression in baseline function. The LAC minimally affected baseline function and caused minimal changes in cardiac hemodynamics with stimulation. The RAC, however, combined the best of both situations. The initial depression of function in the static state was minimal, whereas the augmentation of ventricular function in the dynamic state was significant. The dynamic effects of all of these wraps were not due to changes in systolic preload, as there were no significant differences in left atrial mean pressure with static or dynamic cardiomyoplasty.

Comment

Clinical review of patients with left latissimus cardiomyoplasty has shown that those patients with compromised biventricular function do not fare as well as those with isolated left ventricular failure. Impaired right ventricular ejection fraction has been found to be a predictor of poor outcome with clinical left latissimus cardiomyoplasty [10]. Previous canine experiments with right latissimus cardiomyoplasty applied to the right ventricle have shown improvements in right-sided variables [11, 12]. Bilateral ventricular support has been achieved with the use of a hybrid right latissimus cardiomyoplasty and a mechanical left ventricular assist device [13]. The concept of bilateral cardiomyoplasty was an effort to alleviate right ventricular function as a risk factor by providing biventricular compression of the heart.

Bilateral latissimus dorsi cardiomyoplasty was first hypothesized by Chachques and associates [5]. The procedure was subsequently developed simultaneously by Stephenson's group [8] and our own [7] using different pacing circuits. Significant improvements in global ventricular function were demonstrated by both groups. This study was undertaken to determine the mechanism by which the BAC produces changes in the hemodynamic function of both ventricles. This was done through an analysis of the component parts (LAC and RAC) of the BAC and a search for possible synergy between these two flaps.

Some initial depression of cardiac function occurred

with each type of cardiomyoplasty. However, the mechanism and duration of this disturbance was not investigated. It is our impression that this is a temporary situation caused by displacement of the very mobile canine heart from its normal position when the cardiomyoplasty is performed. However, additional research is needed to evaluate this further. The static BAC caused the largest initial disturbance, which made it easier to demonstrate improvements with stimulation. That is, the hemodynamic changes that occur for a given amount of force applied by contraction of the latissimus dorsi are greater for a depressed ventricle than a normal one. The static LAC and RAC caused minor changes in baseline function, but improvements were seen with dynamic stimulation.

We and others have previously published experimental data that show a left latissimus cardiomyoplasty can improve left ventricular function. The design of these earlier studies was different from the present one in that animals with severe acute heart failure were used. Hemodynamic changes were again more easily demonstrated on these depressed ventricles. The present study tested three types of cardiomyoplasty in each of several animals with normal cardiac function. Although the clinical application of cardiomyoplasty is for patients with heart failure, it would seem that hemodynamic augmentation in a nondepressed ventricular model would be a more stringent test of cardiomyoplasty function.

The synergy between the LAC and RAC that was hypothesized before this experiment was not found. The primary mechanism of biventricular compression produced by BAC is due mostly to the effects of the RAC. In fact, the dynamic RAC produced biventricular hemodynamic improvement not significantly different from that of the BAC. The LAC produced only minimal changes in left ventricular function, which were smaller than those seen with the RAC.

The combination of minimal initial hemodynamic disturbance and maximal biventricular augmentation makes the RAC an attractive procedure for clinical application. Neither the static nor the dynamic LAC caused any large changes in cardiac function. The initial disturbances caused by the static BAC might not be tolerated by a patient with heart failure, especially during the 6-week conditioning period required after the procedure. In addition, performance of a BAC would be a long and complex operation.

There are several possible explanations for the effects of the dynamic RAC. It has previously been shown that anterior positioning of the bulk of latissimus muscle provides improved dynamic augmentation [9]. Ventricular augmentation by the RAC is dependent on contraction of the well-vascularized proximal flap. The distal portion of the right latissimus muscle acts only as an anchor, which converts linear muscular contraction into ventricular compression. Alignment of muscular fibers parallel to the intraventricular septum provides better shortening in the anterosuperior diameter of the left ventricle, which may be important to cardiomyoplasty success [14]. The

RAC achieves both of these goals (see Fig 3). In addition, the fan-shaped spread of the right muscle allows complete biventricular coverage when applied in this slinglike fashion. Finally, contraction of the RAC pulls the ventricle in a direction nearly parallel to the net vector of blood flow through the aortic valve, which might be a more efficient method to assist the left ventricle.

The major limitation of this experiment is that it was an acute study that used animals with normal ventricular function and unconditioned latissimus dorsi muscles. As such, the results cannot be readily extrapolated to the clinical realm of failed ventricles with conditioned cardiomyoplasties. The study was performed in an acute fashion so that direct comparisons of each type of wrap could be made in the same animal. Chronic studies are now in progress to evaluate the hemodynamic effects of several types of cardiomyoplasty in animals with impaired ventricular function. There will likely be some loss in muscle strength with chronic stimulation, but studies from this laboratory show that the change is relatively small [15]. It is difficult to improve the function of a normal ventricle. The effects of cardiomyoplasty should be more readily demonstrated in the chronic state if the animals have some impairment of cardiac function.

In summary, these data show that the static BAC depresses cardiac function, but dynamic BAC results in biventricular augmentation. The LAC has minimal effects on baseline function but causes minimal changes in cardiac hemodynamics with stimulation. The RAC, however, combines the best of both situations. It minimally depresses the native hemodynamics of the ventricles in its static state while providing superior augmentation of ventricular function in its dynamic state. The RAC may be solely responsible for the hemodynamic effects seen with BAC. A single RAC can provide the benefits of the BAC without the complexity and initial hemodynamic disturbance associated with BAC.

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Skeletal Muscle Ventricles: Left Ventricular Apex to Aorta Configuration

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Skeletal muscle ventricles (SMVs) were constructed from the latissimus dorsi muscle in 6 dogs. After 3 weeks of vascular delay followed by 6 weeks of 2-Hz continuous electrical conditioning, a valved conduit was placed between the left ventricular apex and the SMV and a second valved conduit, between the SMV and the aorta. The SMV was stimulated to contract during diastole at a 1:2 ratio with the heart. The SMV pumped 47% of the systemic blood flow initially (0.73 ± 0.23 versus 1.54 ± 0.42 L/min) and 40% after 3 hours. Skeletal muscle ventricle stimulation resulted in a 58% increase in mean

diastolic pressure initially (52 ± 9 to 82 ± 11 mm Hg; $p < 0.05$) and a 73% increase (45 ± 7 to 78 ± 8 mm Hg) after 3 hours of continuous pumping. This was associated with a 68% increase in the endocardial viability ratio initially and a 63% increase at 3 hours. The systolic tension-time index decreased by 26% initially and 25% at 3 hours. This study indicates that the SMV configuration of left ventricular apex to aorta may be particularly suitable for left ventricular assist.

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Various skeletal muscles have been used in attempts to augment cardiac function. One method has been to wrap skeletal muscle directly around the failing heart and then stimulate the skeletal muscle to contract during cardiac systole [1–3]. This method, known as cardiomyoplasty, is currently undergoing phase II clinical trials in the United States. Skeletal muscle has been wrapped directly around the aorta and stimulated during diastole in an attempt to use the muscle as an aortic diastolic counterpulsator [4, 5]. Skeletal muscle pumps have also been coupled with the circulation either directly or indirectly using numerous other ingenious methods [6–17].

In our laboratory, pumping chambers of various shapes have been constructed from canine latissimus dorsi muscle [6–11, 13]. We refer to these blood pumps as skeletal muscle ventricles or SMVs. The purpose of this experiment was to evaluate the pumping characteristics of an SMV coupled between the left ventricular (LV) apex and the ascending aorta.

Material and Methods

Skeletal Muscle Ventricle Construction

Six adult mongrel dogs weighing 16 to 20 kg were operated on in accordance with the "Guide for the Care and Use of Laboratory Animals" published by the National

Institutes of Health (NIH Publication No. 85-23, revised 1985). Anesthesia was induced by intravenous administration of thiamylal sodium (15 mg/kg). The animals were then intubated and placed on a ventilator. Anesthesia was maintained with 2% isoflurane.

Through a left flank incision, the latissimus dorsi muscle was mobilized from the chest wall and surrounding tissues except for its neurovascular pedicle and tendinous insertion to the humerus. A bipolar cuff nerve electrode (Medtronic, Inc, Minneapolis, MN) was placed around the left thoracodorsal nerve for subsequent muscle stimulation. The latissimus muscle was then wrapped approximately 1.5 times around a cylindrical plastic mandrel (diameter, 3.4 cm; volume, 2.5 mL/kg dog weight). A Teflon felt (USCI, Billerica, MA) sewing ring 5 mm wide was used to secure the muscle edge to the base of the mandrel with 5-0 polypropylene. A few interrupted sutures of 4-0 chromic were placed to secure the muscle layers. A 6- to 7-cm portion of the second and third ribs was excised, and the SMV was placed in the apex of the thoracic cavity. The nerve electrode was connected to a neurostimulator (Itrel model 7421; Medtronic, Inc), which was placed through a separate incision under the left rectus abdominis muscle. The wounds were closed in layers.

After a 3-week vascular delay period, the stimulator was activated to deliver 2-Hz continuous stimulation of 210- μ s pulse duration and 1-V amplitude. Electrical stimulation was continued for 6 weeks to induce transformation of muscle fibers to a more fatigue-resistant state [18, 19].

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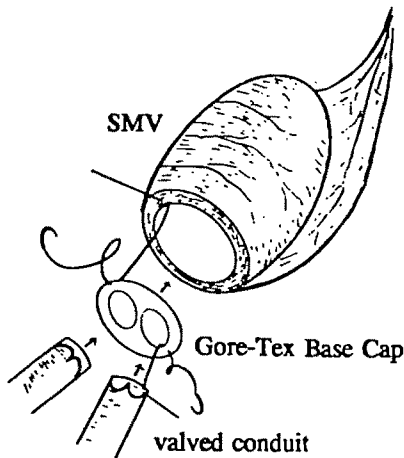


Fig 1. Gore-Tex base cap was used between the skeletal muscle ventricle (SMV) and the valved conduit.

Connection of Skeletal Muscle Ventricle to Circulation

After the 3-week vascular delay and 6-week electrical conditioning periods, a second operation was performed. The animals were anesthetized as before. The heart was exposed through a median sternotomy, and the plastic mandrel was removed from the SMV. After the pericardium was incised, two myocardial leads (sutureless type 6917A-35T; Medtronic, Inc) were placed on the right ventricle for sensing. Two valved conduits were used to connect the SMV to the circulation. The conduits consisted of a woven Dacron tube with a porcine valve 14 mm in diameter (Hancock; Medtronic, Inc). The afferent conduit connected the LV apex to the SMV, and the efferent conduit connected the SMV to the ascending aorta. A circular piece of Gore-Tex material (W. L. Gore & Associates, Inc, Flagstaff, AZ) was used to cap the base of the SMV. Two circular openings 14 mm in diameter were made for inflow and outflow. Each conduit was sutured to an opening in the Gore-Tex base cap with continuous 6-0 polypropylene suture. The valves were placed 1.5 cm from the SMV base. The Gore-Tex base cap was then sutured to the SMV with 4-0 polypropylene suture (Figs 1, 2). Continuous suture of 6-0 polypropylene was used to anastomose the efferent conduit to the aorta.

The afferent conduit was anastomosed to the LV apex without cardiopulmonary bypass. A soft plastic connecting tube (inner diameter, ¼ inch [6.25 mm]; length, ⅝ inch [21.9 mm]; Cobe Laboratories, Inc, Lakewood, CO) was used to couple the LV apex to the afferent conduit. A double pursestring suture of 4-0 braided polyester was placed in the ventricular apex, through which a 1.2-cm incision was made with a No. 10 blade, and the connector was inserted (see Fig 2). A dose of 1,000 units of heparin sodium and 1 mL of 2% lidocaine hydrochloride were administered intravenously before this maneuver. All air was aspirated from the SMV and the conduits, and they then were filled with a solution of 0.9% sodium chloride.

Skeletal Muscle Ventricle Stimulation Protocol

After the SMV was connected to the circulation, a rate-responsive synchronized pulse train stimulator (Prom-

theus; Medtronic, Inc) was connected to the nerve lead and heart-sensing leads. The pacemaker was programmed to deliver a 33-Hz burst of electrical stimulation with a delay of 30% to 35% of the R-R interval to provide diastolic counterpulsation, a burst duration of 30% of the R-R interval, a 2- to 3-V amplitude, and a 1:2 (SMV to heart) contraction ratio.

Measurements

After the SMV was activated to pump blood continuously, SMV function and hemodynamic measurements were assessed hourly for 3 hours. The last dog was followed up for 10 hours. At each hour, measurements were made first with the stimulator on. The stimulator was then turned off, and after 3 minutes of equilibration, measurements were obtained with the stimulator off. The stimulator was then switched on again. The femoral and carotid artery pressures were recorded with a fluid-filled manometer line connected to a transducer. Left ventricular pressure and SMV pressure were measured directly with a 5F microtransducer-tipped catheter (Millar Instruments Inc, Houston, TX). Cardiac output was recorded using a 16-mm ultrasonic flow probe (Transonic Systems Inc, Ithaca, NY) placed around the main pulmonary artery. Flow generated by the SMV was recorded with a 16-mm flow probe positioned around the efferent conduit. Data were collected with a Gould ES 1000B recording and display system. After these acute experiments, all the animals were killed with intravenous KCl while they were under isoﬂurane anesthesia.

Calculation

Cardiac output and SMV output were calculated by integrating the respective flow curves using a digitizing pad

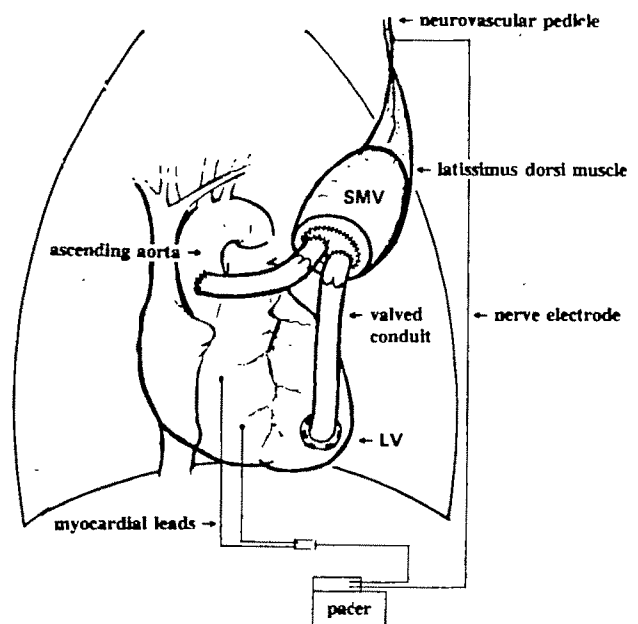
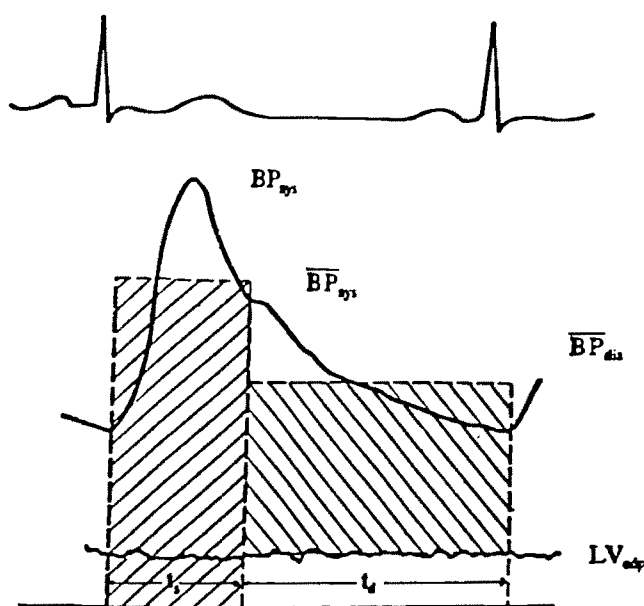


Fig 2. Skeletal muscle ventricle (SMV) connected between the left ventricular (LV) apex and the ascending aorta (intrathoracic position).



EQUATIONS

$$TTI = \overline{BP}_{sys} \times t_s = \text{shaded area}$$

$$EVR = \frac{(\overline{BP}_{dia} - LVedp) \times t_d}{TTI} = \frac{\text{shaded area}}{\text{shaded area}}$$

Fig 3. Calculation of tension-time index (TTI) and endocardial viability ratio (EVR). ($\overline{BP}_{dia}$ = mean diastolic blood pressure; BP_{sys} = systolic blood pressure; $\overline{BP}_{sys}$ = mean systolic blood pressure; $LVedp$ = left ventricular end-diastolic pressure; t_d = diastolic time interval; t_s = systolic time interval.)

(Digi-Pad 5; GTCO Corp, Rockville, MD) linked to a portable computer (T-3200; Toshiba, Irvine, CA). Mean pressure was calculated as the pressure area divided by time. The endocardial viability ratio [20] and systolic pressure tension-time index [21] were calculated from pressure curves as analyzed with the digitizing pad and portable computer (Fig 3). The stroke work was calculated as the product of the stroke volume and mean arterial pressure. Comparison of the mean diastolic arterial blood pressure with the stimulator off versus on was used to assess SMV diastolic augmentation.

For the purpose of presenting data, the "presumed" LV output (with the SMV on) was calculated as SMV flow subtracted from pulmonary artery flow. This represents the blood flow expected to cross the aortic valve and does not take into account the blood that enters the left ventricle and flows passively or that is pumped into the SMV.

Data are expressed as the mean $\pm$ the standard deviation. Statistical analysis was performed by paired *t* test using RS/1 software (copyright 1986, Bolt Beranek and Newman Inc, Cambridge, MA).

Results

The SMV contraction rate, the peak pressure generated by the SMV, and the end-diastolic pressure remained relatively constant over 3 hours (Table 1). The SMV stroke volume, which was 92% of the cardiac stroke volume initially (13.2 ± 5.4 versus 14.3 ± 4.6 mL), increased 10% at 1 hour (14.5 ± 4.6 mL) and then decreased to 80% of its initial volume after 3 hours (10.6 ± 3.5 mL). As the SMV contraction rate was half of the native heart rate, the SMV output was initially 47% of the systemic blood flow (pulmonary artery flow) (0.73 ± 0.23 versus 1.54 ± 0.42 L/min) and 40% of the systemic blood flow at 3 hours (0.60 ± 0.15 versus 1.52 ± 0.62 L/min). These changes are represented in Figure 4A. Initially, the SMV stroke work was 91% of that of the left ventricle ($0.92 \pm 0.35 \times 10^6$ versus $1.01 \pm 0.39 \times 10^6$ ergs). After 3 hours of continuous pumping, the SMV stroke work was 72% of its initial value ($0.66 \pm 0.14 \times 10^6$ ergs).

The hemodynamic variables measured initially and at each hour with the SMV stimulator off and on are recorded in Table 2. At the beginning, SMV stimulation resulted in a 58% increase in mean diastolic arterial blood pressure (52 ± 9 to 82 ± 11 mm Hg; $p < 0.05$). Over the next 3 hours, the augmentation with SMV stimulation increased to 62%, 66%, and 73.3% (Fig 4B). Because the calculation of the endocardial viability ratio is dependent on the average pressure during diastole, the mean diastolic arterial blood pressure augmentation was associated with a 68% increase in this ratio initially (1.12 ± 0.08 versus 1.88 ± 0.15 ; $p < 0.05$) and 66%, 62%, and 63% increases at 1 hour, 2 hours, and 3 hours, respectively (Fig 4C).

Throughout the 3-hour experiment, there was an average 6% increase in both the mean arterial blood pressure and the systemic blood flow with the SMV stimulator on

Table 1. Function of Skeletal Muscle Ventricle

Variable	Start	1 Hour	2 Hours	3 Hours
SMV contractions (no./min)	55 ± 7	55 ± 6	55 ± 6	54 ± 5
SMV peak systolic pressure (mm Hg)	91 ± 10	91 ± 9	84 ± 16	88 ± 7
SMV end-diastolic pressure (mm Hg)	8 ± 3	8 ± 4	9 ± 5	9 ± 4
SMV stroke volume (mL)	13.2 ± 5.4	14.5 ± 4.6	11.7 ± 6.9	10.6 ± 3.5
SMV stroke work (10^6 ergs)	0.92 ± 0.35	0.86 ± 0.35	0.74 ± 0.32	0.66 ± 0.14
SMV output (L/min)	0.73 ± 0.23	0.71 ± 0.35	0.63 ± 0.33	0.60 ± 0.15

SMV = skeletal muscle ventricle.

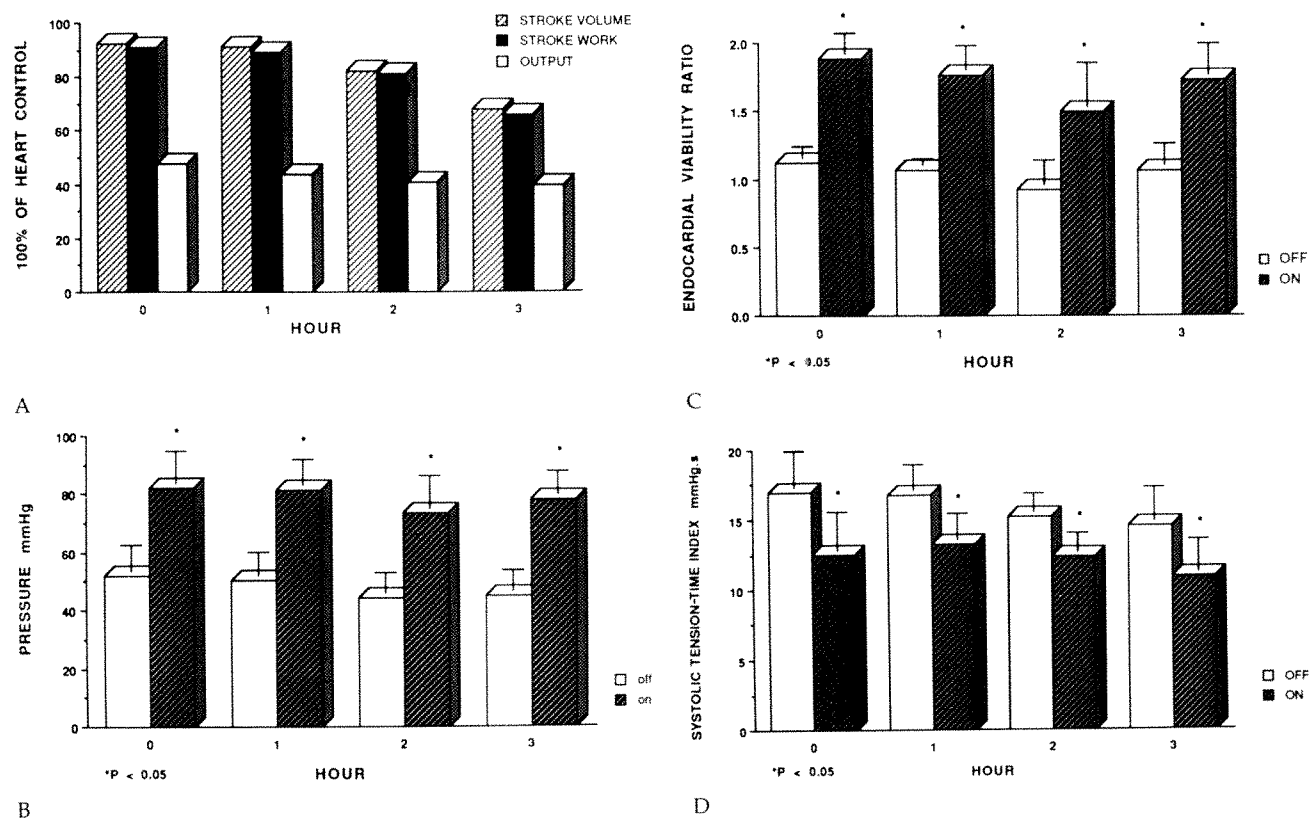


Fig 4. (A) Stroke volume, stroke work, and output of skeletal muscle ventricle (SMV) compared with native heart control (SMV off). (B) Diastolic arterial pressure change with SMV contraction off and on. (C) Increases in endocardial viability ratio with SMV contraction on. (D) Decreases in systolic tension-time index with SMV contraction on.

versus off. In contrast, the systolic arterial blood pressure was consistently decreased during the 3 hours with the SMV stimulator on versus off. Consequently, the mean arterial blood pressure during systole was decreased. The systolic tension-time index was decreased, initially by 26% (16.9 ± 2.7 versus 12.5 ± 3.3 mm Hg · s; $p < 0.05$) and after 3 hours, by 25% (Fig 4D).

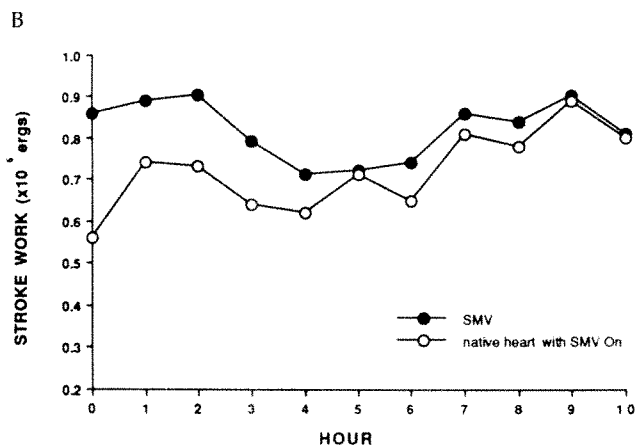
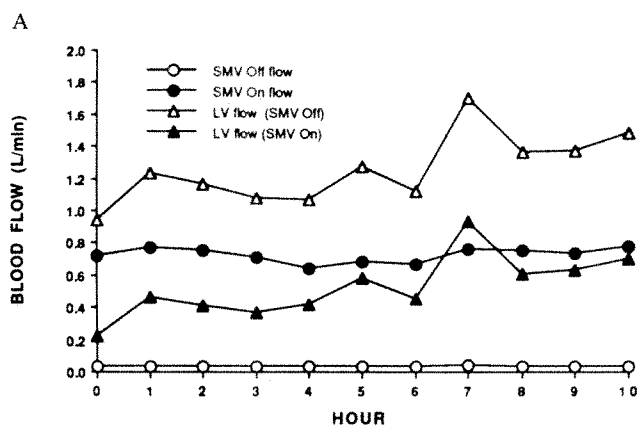
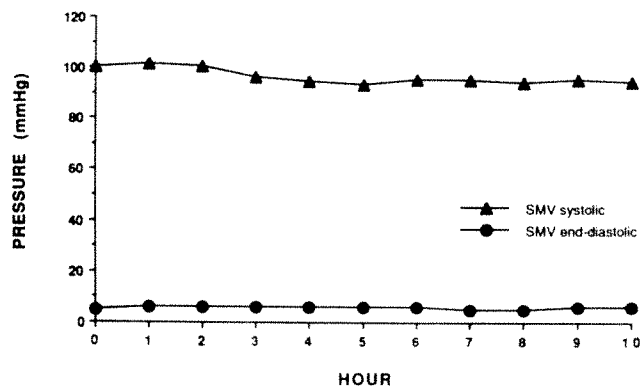
The single animal studied over 10 hours had similar decreases in stroke volume, SMV output, and stroke work during the initial 3 to 4 hours. However by 7 hours, there was an increase in these variables that exceeded their original values (Fig 5). This change was achieved by a decreased systolic arterial pressure (92 ± 11 versus 82 ± 10 mm Hg; $p < 0.05$). The SMV pressures remained

Table 2. Hemodynamic Variables During 3-Hour Study With Stimulation Off and On

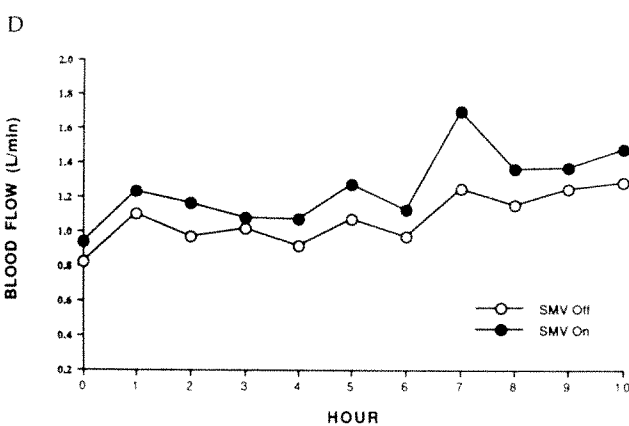
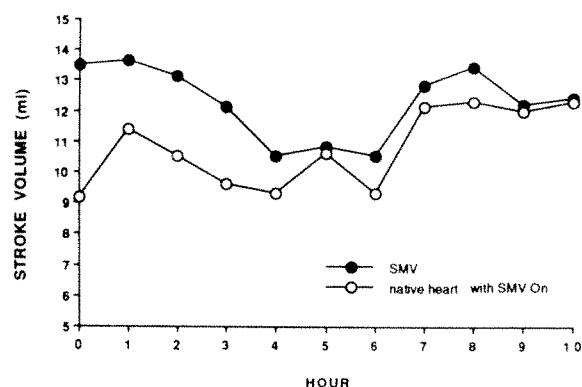
Variable	Start		1 Hour		2 Hours		3 Hours	
	Off	On	Off	On	Off	On	Off	On
HR (beats/min)	109 ± 13	109 ± 13	111 ± 12	111 ± 12	110 ± 11	110 ± 11	109 ± 11	109 ± 11
SV (mL)	13.1 ± 4.8	14.3 ± 4.6	13.6 ± 1.8	14.5 ± 2.6	13.5 ± 4.6	14.3 ± 4.8	13.5 ± 5.5	15.7 ± 6.2
BP _{sys} (mm Hg)	92 ± 11	82 ± 10 ^a	89 ± 8	81 ± 9 ^a	91 ± 5	83 ± 6 ^a	89 ± 6	80 ± 7 ^a
BP _{dia} (mm Hg)	52 ± 9	82 ± 11 ^a	50 ± 8	81 ± 9 ^a	46 ± 7	73 ± 11 ^a	45 ± 7	78 ± 8 ^a
MAP (mm Hg)	66 ± 9	69 ± 11 ^a	64 ± 7	67 ± 9	59 ± 6	64 ± 10 ^a	60 ± 7	64 ± 8 ^a
LVP (mm Hg)	87 ± 14	80 ± 13 ^a	85 ± 10	78 ± 11 ^a	82 ± 8	76 ± 7 ^a	84 ± 9	75 ± 6 ^a
LVEDP (mm Hg)	5.3 ± 1.8	5.1 ± 1.5	0.2 ± 2.5	4.6 ± 1.9	4.8 ± 2.6	4.4 ± 2.3	5.3 ± 2.1	5.6 ± 1.3
Q _{sys} (L/min)	1.43 ± 0.46	1.54 ± 0.42 ^a	1.49 ± 0.19	1.63 ± 0.26 ^a	1.49 ± 0.48	1.54 ± 0.52	1.45 ± 0.56	1.52 ± 0.62
TTI (mm Hg · s)	16.9 ± 2.7	12.5 ± 3.3 ^a	16.7 ± 1.8	13.2 ± 2.1 ^a	15.1 ± 1.3	12.3 ± 1.1 ^a	14.5 ± 2.3	10.9 ± 2.0 ^a
EVR	1.12 ± 0.08	1.88 ± 0.15 ^a	1.06 ± 0.05	1.76 ± 0.17 ^a	0.92 ± 0.18	1.49 ± 0.32 ^a	1.06 ± 0.16	1.73 ± 0.22 ^a

^a Significance: $p < 0.05$ by paired t test.

BP_{dia} = mean diastolic carotid artery pressure; BP_{sys} = systolic carotid artery pressure; EVR = endocardial viability ratio; HR = heart rate; LVEDP = left ventricular end-diastolic pressure; LVP = left ventricular peak pressure; MAP = mean carotid artery pressure; Q_{sys} = systemic blood flow; SV = averaged left ventricular stroke volume with skeletal muscle ventricle functioning 1:2 with left ventricle (includes blood entering left ventricle and flowing either across aortic valve or into skeletal muscle ventricle); TTI = systolic tension-time index.



C



E

Fig 5. Measurements for dog followed up for 10 hours: (A) skeletal muscle ventricle (SMV) pressure; (B) SMV flow measured with flow probe during 1:2 pumping ratio with the heart, and "presumed" left ventricular (LV) blood flow across aortic valve; (C) SMV and native heart stroke work (LV stroke work was calculated as mean aortic pressure times pulmonary artery flow divided by heart rate; pulmonary artery blood flow should equal the volume of blood entering the left ventricle and flowing out); (D) SMV stroke volume; and (E) main pulmonary artery flow.

constant from 3 hours to 10 hours. Representative hemodynamic recordings at 3 hours and 10 hours are seen in Figure 6.

Comment

Skeletal muscle ventricles of different shapes have been tested in our laboratory acutely and chronically. These muscle pumps have been evaluated in mock circulation circuits and as assist devices for both the pulmonary and systemic circulations [6-11, 13, 22]. The SMV configuration with valved conduits coupled between the left ventricle and the aorta presented herein has not previously been evaluated by our group. Although this was an acute

in-circulation experiment, the hemodynamic results are the best we have obtained in that 40% to 47% of the systemic blood flow was supplied by the SMV.

Where SMVs have been used as aortic diastolic counterpulsators, the aortic blood flow has usually been routed directly through the SMV [6-9, 16, 22]. We have connected the SMVs to the ascending aorta, but more commonly to the descending aorta, for diastolic counterpulsation. The stroke volume pumped by these SMVs has been in the range of 4 to 9 mL. The percent of LV blood pumped by these SMVs has been in the range of 17% to 20% [22, 23]. Canine SMVs do not seem to tolerate pumping rates of more than 100 contractions per minute for prolonged periods. Therefore, they are generally stim-

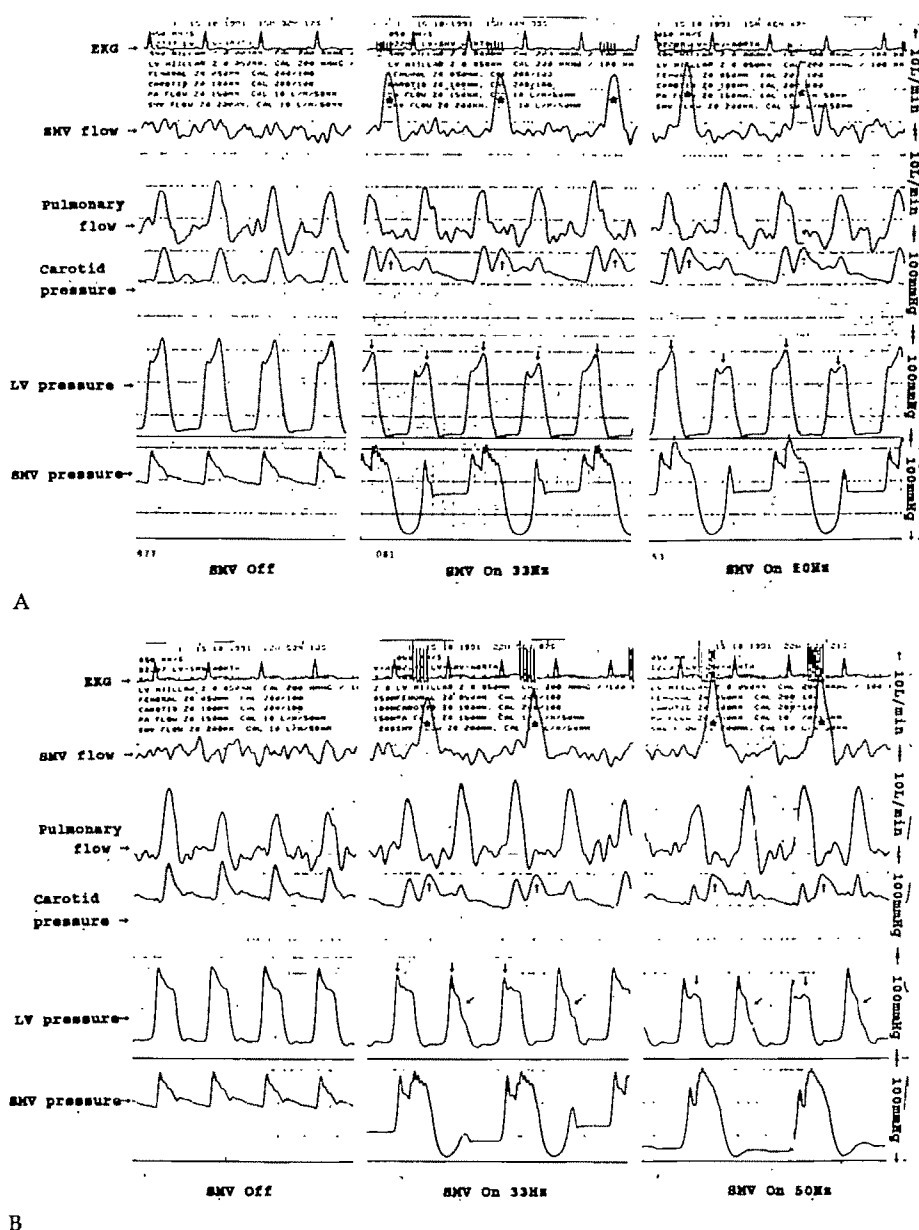


Fig 6. Hemodynamic recordings for the last dog at (A) 3 hours and (B) 10 hours with skeletal muscle ventricle (SMV) contraction off and on. (EKG = electrocardiogram; * = SMV stroke volume; ↑ = diastolic arterial pressure augmentation; and ↓ = left ventricular [LV] systolic pressure decrease; ↙ = LV tension-time decrease.)

ulated at a 1:2 ratio with the heart. For this reason, even when the stroke volume of the SMV is equal to that of the left ventricle, the power output is less.

These SMVs have functioned effectively as aortic counterpulsators for several months without evidence of thromboembolism. In 1 animal, an SMV pumped blood effectively for 27½ months [24]. Because skeletal muscle is less compliant than cardiac muscle, using the SMV as an aortic diastolic counterpulsator has the advantage that the SMV is supplied with a high filling pressure. These SMVs contract during diastole and relax during systole; therefore, the lowest pressure in the SMV cavity tends to range between 70 and 80 mm Hg. It is possible that constant pressures of this magnitude may be too high and hamper blood flow within the muscle layers of the SMV or cause other damage to the muscle over time.

We [10] have also evaluated SMVs pumping blood from

the left atrium to the aorta. This configuration requires two valves: one between the left atrium and the SMV and one between the SMV and the aorta. The SMV in this configuration also contracts during cardiac diastole, because if it pumped during cardiac systole, it would be pumping against LV ejection. In animals with normal hearts, the left atrial pressures have remained in the range of 14 to 16 mm Hg over 3-hour experiments. The percentage of the systemic blood flow pumped by the SMV has been in the range of 21% to 27% of the cardiac output with SMVs pumping at a ratio of 1:2 with the heart. To date, we have not been successful in converting the left atrium to aorta SMV configuration into a chronic model. Higher filling pressures may be required over longer periods. It is possible that with a stable LV failure model, where filling pressures are higher, this configuration would function effectively for prolonged periods.

There are both experimental and clinical reports [25-27] in which blood has been routed, without an auxiliary pump, from the LV apex to the aorta with a valved conduit. Clinically, this valved-conduit technique has been used for the treatment of hypertrophic obstructive cardiomyopathies and idiopathic hypertrophic subaortic stenosis.

A variety of mechanical pumps have also been used to route blood flow from the LV apex to the aorta to bridge patients awaiting heart transplantation and to treat patients for other conditions causing profound LV failure [28].

Using an SMV to pump blood between the left ventricle and the aorta, as was done in this experiment, might overcome some of the potential problems encountered with other SMV configurations. As the SMV with the left ventricle to aorta configuration predominantly fills during LV systole, the potential problem of inadequate filling pressures with the left atrium to aorta configuration is overcome. In addition, because the pressure in the SMV cavity is equal to the LV end-diastolic pressure during a portion of the SMV pumping cycle, there is likely to be improved blood flow in the muscle layers of the SMV compared with the aortic diastolic counterpulsator configuration [23, 29, 30]. Other potential problems of continuous high pressure in the aorta to aorta configuration might also be avoided.

In other recent experiments [9], comparison was made between placing the SMV inside the thoracic cavity and placing it in the more conventional position on the chest wall. The intrathoracic SMVs were found to be more compliant and generated greater stroke work than those placed on the chest wall. The SMVs in the present study therefore were placed inside the thoracic cavity.

The Gore-Tex base cap used in this model also may have contributed to its success. Because the openings for the afferent and efferent conduits were properly sized, SMV inlet and outlet obstruction was likely avoided. Such obstruction could have occurred earlier when the base cap was not used.

During this 3-hour experiment, the systolic tension-time index was significantly lower with the SMV on versus off, which indicates that the myocardial oxygen requirement was reduced [21]. The endocardial viability ratio was significantly increased with the SMV on versus off, which indicates that the subendocardial blood flow was improved during SMV pumping [20].

Earlier, Brister and colleagues [31] and Stevens and co-workers [16] used unconditioned rectus muscle to pump blood between the left ventricle and the aorta. Muscle was wrapped around a bladder with a single valve. The model used by Brister's group had an afferent valve and that of Stevens's group, a valve in the efferent limb of the conduit. Brister and associates apparently did not measure flow but did observe augmentation of diastolic aortic pressures. In the acute heart failure model of Stevens and colleagues, cardiac output was initially increased 31% over control while the muscle pump was functioning, but only 8% over control at 1 hour. In the current experiment, cardiac output increased only slightly

with the SMV functioning. This may have been because our animals had normal hearts, whereas the animals in the study by Stevens and co-workers were in heart failure.

Although cardiac output in the current experiment improved only slightly with the SMV pumping, 47% of the systemic blood flow was pumped by the SMV rather than the left ventricle. Although the percentage of blood pumped by the SMV compared with that pumped by the left ventricle did decrease over the 3-hour study (47% initially to 40% at 3 hours), the deterioration in function was not nearly as rapid as in the study by Stevens's group [16]. This may have been because they used unconditioned muscle, whereas the muscle in our study had been electrically conditioned to make it more fatigue-resistant. Electrical conditioning of a muscle also causes the muscle to lose some strength. This could explain why the initial increase in cardiac output seen in the study by Stevens and associates was greater than that seen in our study. The fact that Stevens and associates used a different muscle, ie, rectus versus latissimus, also may have contributed to this difference.

In the animal followed up for 10 hours, SMV function stabilized after 3 to 4 hours. From previous experience, this stabilization in function over several hours indicates that about the same level of SMV performance is likely to occur in a chronic setting [32].

Voytik and co-workers [33] used electronics to model the human circulation as resistive-capacitive networks, with pressures as voltages, blood flow as electrical current, cardiac valves as diodes, heart chambers and great vessels as capacitors, and capillary beds as resistors. Their data from the models of different SMV configurations demonstrated the superiority of the LV apex to aorta design compared with an aorta to aorta or atrium to aorta design. The LV apex to aorta model provided greater augmentation of the total cardiac output, greater reduction of the mean LV power, and greater mean SMV power in both the normal heart and a heart failure simulation.

There are several limitations to the current study. Two valves were used in this model, which makes it a more efficient pump system but gives it the potential for more complications long term. This was a short-term study, and it is not yet known whether the same level of SMV performance can be sustained in long-term studies. In this study the animals had normal hearts, and it is not known how well this SMV system would perform during heart failure, which in fact, would be more clinically relevant. However, it is encouraging that in the experiments by Stevens and colleagues [16] discussed earlier, the animals were in heart failure, and systemic blood flow increased by 31% as opposed to 6% in our study.

Also, the true unloading effect that the SMV has on LV function is not completely clear at this point. We measured pulmonary flow and SMV blood flow as well as aortic, LV, and SMV pressure. By subtracting SMV flow from pulmonary artery flow, "presumed" LV output, the amount of blood in liters per minute that we assumed crossed the aortic valve, was obtained. We do not know that the same amount of blood that flowed across the pulmonary artery should have gone into the left ventricle

and then would have either been pumped into the aorta or been pumped or flowed passively into the SMV. It is unclear how much work was required by the left ventricle to fill the SMV. We do know that very little blood was ejected by the left ventricle during systole through the SMV into the aorta when the SMV was either off or on, as witnessed by the SMV flow traces in Figure 6.

In conclusion, this study demonstrates that the SMV configuration of LV apex to aorta with two valved conduits may be particularly suitable for LV assist. The SMV decreases LV work and oxygen consumption while increasing myocardial blood flow. This benefit was achieved by (1) SMV diastolic augmentation, (2) presystolic LV unloading into the SMV, and (3) valves that reduced regurgitant flow. More importantly, although systemic blood flow increased only slightly during SMV contraction, almost half of the systemic blood flow was pumped by the SMV rather than the left ventricle.

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Prophylactic Digitalization Fails to Control Dysrhythmia in Thoracic Esophageal Operations

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A prospective, controlled, randomized study of 80 patients undergoing esophageal operations was undertaken, in which one group of patients was given digoxin and the other was not. The incidence of cardiac dysrhythmia was compared in each group. Twenty-six patients underwent operation for benign disease. Equal numbers were digitalized or not and no dysrhythmias occurred.

Fifty-four patients underwent operation for malignant disease. Of 26 in the group digitalized, 12 suffered dysrhythmia (46%). Of 28 not digitalized, 9 suffered dysrhythmia (32%). Overall, 39% of patients with malignant disease suffered a dysrhythmia compared with none with benign disease ($p < 0.002$ by χ^2).

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The role of thoracic surgery in the treatment of benign and malignant disease of the esophagus has been established since the work of Heller [1] and Torek [2]. Digitalis was discovered and first used successfully by William Withering of Birmingham more than 200 years ago. It was first used in the treatment of heart failure associated with atrial fibrillation in 1911 [3]. A specific and significant association of atrial fibrillation with thoracic surgical procedures [4-6] led to the suggestion that digitalis was indicated as a prophylactic measure [7] to prevent this complication. This became established for both pulmonary and esophageal thoracic operations, although the etiology of the arrhythmias remains unclear [8]. There have been contradictory reports on the effectiveness of prophylactic digoxin [9-11], although none specific to esophageal thoracic operations. The role of digitalis has come under review with awareness of the potential of the drug itself to induce arrhythmia and the availability of safer alternatives [12]. This led us to reevaluate the role of prophylactic digoxin in esophageal thoracic operations for both benign and malignant disease.

Patients and Methods

Eighty consecutive patients who underwent elective thoracic esophageal operations were studied in an open, randomized clinical trial. Preoperative assessment included pulmonary function tests, electrocardiography, and measurement of urea and electrolyte levels and arterial blood gas tensions to determine suitability for operation. Patients with inadequate respiratory reserve, hypoxemia when breathing room air, or electrocardiographic evidence of myocardial infarction or a current

dysrhythmia and patients who were being treated for dysrhythmia were excluded from the study. Ten patients with documented myocardial disease entered the study. Those with malignant disease were well matched for age, sex, site of tumor, and operative intervention.

Patients were randomly allocated to preoperative digoxin (D) or no treatment (ND). A standard regimen of 500 μg at 18.00 hours and 22.00 hours the day before operation, followed by 250 μg with premedication, was given. Postoperatively, 250 μg digoxin was given daily for 9 days and adjusted according to serum levels (radioimmunoassay, Amerlex kit, Amersham, England; reference range, 1 to 2 $\mu\text{g/L}$).

Serum digoxin levels were measured immediately preoperatively and 6 hours after the oral dose on days 1, 3, 5, and 7 postoperatively. One of us participated in each procedure specifically to record details and assess patients. Constant screen monitoring of the electrocardiogram was chosen in preference to Holter monitoring to allow analysis of factors such as hypoxemia and hypokalemia to be assessed at the onset of a dysrhythmia. This commenced at the time of anesthetic induction and continued for at least 4 days, after which 12-lead electrocardiography was performed on alternate days. In the operative and recovery periods this was recorded by us. Patients were monitored by staff visually from the electrocardiographic trace, which had a preset dysrhythmia alarm after their return to the ward. Tracings were recorded automatically when a dysrhythmia occurred and analyzed by us, and subsequently by a cardiologist. Serum potassium and arterial blood gas tensions were determined at the time of onset of a dysrhythmia and treated as appropriate.

A dysrhythmia was defined as the first electrocardiographic rhythm abnormality recorded that persisted across one full monitor screen. Subsequent episodes of dysrhythmia in the same patient, and that group with

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Table 1. Incidence of Dysrhythmia^a

Variable	Benign		Malignant	
	Digoxin	No Digoxin	Digoxin	No Digoxin
No. of Patients	13	13	26	28
Dysrhythmia				
No. of Patients	0	0	12	9
Percentage	0	0	46	32

^a $p < 0.002$ by χ^2 .

serum digoxin levels greater than 2 $\mu\text{g/L}$ who had bigemini, multifocal ventricular ectopics or T wave changes, were excluded from analysis. Statistical analysis was by χ^2 using Yates' correction where appropriate.

Results

Overall mortality was 6.25%. Five patients died within 30 days of operation: 2 had esophageal carcinoma resected by left thoracotomy and died postoperatively as a consequence of anastomotic breakdown, with two further deaths as a result of respiratory failure; one patient underwent left thoracotomy and repair of hiatus hernia by the Belsey Mark IV procedure and died 7 days postoperatively as a consequence of aspiration bronchopneumonia. The average age of those who died was not significantly different from their group as a whole, being 55 years for patients with benign disease and 69 years for patients with malignant disease. Of those given digoxin, 3 patients (4%) had serum digoxin levels below the therapeutic range immediately preoperatively.

Overall, 21 patients suffered cardiac dysrhythmia (26%) but none with benign disease. Fifty-four patients underwent operation for malignant disease. Of 26 in group D, 12 suffered dysrhythmia (46%) compared with 9 of 28 in group ND (32%). In the malignant disease group, 39% of patients suffered cardiac dysrhythmia compared with none with benign disease ($p < 0.002$ by the χ^2) (Table 1).

All the dysrhythmias that occurred would be expected to be prevented by or related to digoxin therapy. The average age of patients with malignant disease in group D was 66 years and in group ND, 74 years ($p < 0.02$). That there were no dysrhythmias in those patients undergoing thoracotomy for benign disease suggests that thoracotomy alone does not induce this complication. There was no difference in the incidence of dysrhythmia for each operative procedure. Some 76% of patients who had dysrhythmias at any time during follow-up had their initial dysrhythmic episode before the sixth postsurgical hour (Table 2). Of the patients who suffered dysrhythmia, all in group D required active intervention whereas those in group ND did not. In no case could the onset of dysrhythmia be related to hypoxia or serum potassium levels.

Comment

This randomized study reports the incidence of cardiac dysrhythmia in patients undergoing elective thoracic

esophageal operations for benign and malignant disease. Previous reports of such patients have been included in those undergoing thoracic operation mainly for pulmonary disease, but the interpretation of these reports is complicated by their retrospective nature and the variability of methods and groups under study [5, 13]. This study has confirmed cardiac dysrhythmia as a significant complication only for that group with malignant disease and suggests no benefit from prophylactic digitalization. All those in group D required intervention to treat their complication, whereas those in group ND did not.

These findings suggest a negative impact of digoxin because 46% of patients in group D, compared with 32% in group ND, with malignant disease suffered dysrhythmias. Although not a statistically significant difference ($p = 0.29$), this negative impact is substantiated by the requirement for intervention once dysrhythmia occurs. In group D, 7 patients suffered atrial fibrillation with uncontrolled ventricular rate resulting in lowering of mean arterial blood pressures. Three patients had persistent supraventricular tachycardia resulting in lowering of mean perfusion pressures. The other 2 patients had a combination of reentry arrhythmias resulting in multiple atrial and ventricular ectopics. The 9 patients in group ND who suffered dysrhythmia did not require intervention. Atrial fibrillation occurred in 6 patients without hemodynamic effect. One patient had supraventricular tachycardia controlled by carotid massage, and the other 2 patients had supraventricular paroxysmal tachycardia without hemodynamic effect. Seven (58%) of the 12 who required intervention suffered dysrhythmias before the sixth postoperative hour.

We believe the methods used in this study have allowed us to detect high incidence of cardiac dysrhythmia in 39% of those with malignant disease and to identify the operative and first 6-hour postoperative period as the most common time of onset. By identifying this period we can adjust our efforts to detect and control this complication. Several factors have been identified in the etiology of cardiac dysrhythmias in patients undergoing thoracic operations but none specific to esophageal operations [6, 12, 13]. In patients with benign disease only 1 case of dysrhythmia has previously been reported [14], indicating that thoracotomy per se does not induce this complication. There is a significant difference in age between those with benign and those with malignant disease ($p < 0.05$), which may partly explain this difference.

Increased vagal tone, hypoxia, and direct invasion by tumor have been thought to be important in those patients undergoing pulmonary operations [1, 6]. In this study the onset of dysrhythmia could not be related to

Table 2. Onset of Dysrhythmia in Malignant Disease

Dysrhythmia	Number	Percentage
Total dysrhythmias	21	39
Intraoperative	11	52
Up to 6 hours postoperative	5	24

hypoxia, operative manipulation, or specifically to site of tumor. In addition, there was no clear correlation in relation to length of operation or magnitude of dissection in each individual. In those patients suffering dysrhythmia, tumor was identified in the carinal nodes in 4 patients (7%). This, and the demonstration that the majority of cardiac dysrhythmias occur on the day of operation, indicate that other factors may be more significant in thoracic esophageal operations. All anesthetic agents currently used are potentially dysrhythmogenic. Limitation in the efficacy of digoxin, particularly in the older age group, has been suggested [12], emphasizing the dangers of dysrhythmogenicity [15] and toxicity [11]. None of our patients was hypokalemic or in renal failure at onset of dysrhythmia.

In conclusion, this prospective, randomized study in thoracic esophageal surgery has failed to demonstrate benefit from prophylactic digitalization, which is associated with an increased hazard in terms of incidence of cardiac dysrhythmia and its treatment. In addition, we have demonstrated that this complication is confined to patients with malignant disease and is more likely to occur on the day of operation in a generally older age group. Further efforts to identify the factors involved in extended prospective studies by ourselves and others may lead to a useful revision of the role of prophylactic digitalization and examine in detail these initial findings.

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Benefits of Posttransplantation Monitoring of Interleukin 6 in Lung Transplantation

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To determine the predictive diagnostic value of interleukin 6 (IL-6) monitoring in lung and heart-lung transplants, we measured posttransplantation serum IL-6 levels in 17 adult lung or heart-lung transplant recipients. Posttransplantation IL-6 elevation patterns were classified into 4 groups: serum IL-6 level remained negative throughout the monitoring period (group 1; $n = 1$; 6%); several sharp spikes with normal baseline (group 2; $n = 9$; 53%); persistently high level of serum IL-6 (group 3; $n = 3$; 18%); and several sharp spikes of serum IL-6 elevation with abnormally high baseline (group 4; $n = 4$; 24%). One patient without an elevation of IL-6 (group 1) did not experience any episodes of rejection or infection. Nine patients in group 2 had 19 IL-6 spikes, 13 of which

were associated with histopathologically or clinically diagnosed rejection, 3 with acute bronchitis, and 1 with diffuse alveolar damage. Three patients in group 3 had persistent infections including cytomegalovirus infection, toxic megacolon, and repeated bacterial infection during the monitoring period, and 4 in group 4 died within 3 months after transplantation. From this study it appears that a spiked elevation of IL-6 could have a predictive value in diagnosing rejection, and persistently high levels of IL-6 indicate the presence of infection. Thus, IL-6 monitoring is beneficial for lung transplant recipients.

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As lung transplantation becomes a more common therapeutic modality for patients with end-stage lung disease, the demand for timely diagnosis of infection and rejection increases proportionately. Presently, comprehensive diagnoses of rejection episodes in lung transplant patients are based on symptoms that include fever, chest roentgenographic changes, and worsening gas exchanges [1-3]. Histopathological diagnoses from transbronchial biopsies provide distinct information [4], although frequent biopsies are undesirable. Lymphocyte proliferative activity of bronchoalveolar lavage also provides supportive diagnostic evidence of rejection [5, 6] in lung transplant patients. However, in contrast to kidney or liver transplants, there are no adequate plasma or serum parameters to indicate rejection in lung transplant recipients.

Cytokines play a crucial role in mediating biological responses, particularly in self-defense systems. Interleukin 6 (IL-6), a pleiotropic cytokine, is released primarily by activated macrophages in addition to activated T lymphocytes followed by antigen presentation [7, 8]. In our previous study, IL-6 seemed to reflect the magnitude of a recipient's immune responses after lung transplantation [9].

Thus, we meticulously monitored serum IL-6 levels in lung transplant recipients to study whether or not an

elevation of serum IL-6 could provide any predictive value in diagnosing posttransplantation infection or rejection episodes.

Material and Methods

Patients

Subjects of this study, performed at Presbyterian University Hospital, University of Pittsburgh, between November 1990 and May 1991, were 17 adults aged 26 to 56 years (mean age, 38.9 years) who received either single-lung (6 patients), double-lung (9 patients), or heart-lung transplants (2 patients). The demographics of patient diagnoses are shown in Table 1. All grafts were harvested in a similar fashion and stored in Euro-Collins solution, and all patients received similar perioperative intensive care, as described earlier [1].

Immunosuppression

All patients received cyclosporine A with dosage adjusted to maintain blood levels at between approximately 700 ng/mL and 1,000 ng/mL (whole blood radioimmunoassay; Sandoz Pharmaceuticals, East Hanover, NJ). Methylprednisolone was administered three times (125 mg each) during first day after transplantation. Steroids were withheld during the first 2 postoperative weeks, after which prednisone administration was instituted at a maintenance dose of 20 mg/day. During this period, patients received a 3- to 5-day course of rabbit antithymocyte globulin. Azathioprine (2 to $3 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$) was

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Table 1. Demographics of 17 Lung Transplant Patients

Disease	N	Mean Age (y)	Sex M:F	Transplant		
				Single-Lung	Double-Lung	Heart-Lung
Primary pulmonary hypertension	2	38.5	1:1	0	2	0
Secondary pulmonary hypertension	5	33.4	1:4	1	2	2
Emphysema (α_1 -antitrypsin deficiency)	5 (3)	48.4	5:0	5	0	0
Lung fibrosis (cystic fibrosis)	5 (4)	34.4	5:0	0	5	0
Total	17	38.8	12:5	6	9	2

adjusted to maintain an absolute number of blood neutrophils greater than $2 \times 10^9/L$ ($2,000/\mu L$).

Diagnosis of Rejection

Biopsies were performed routinely at 2 and 4 weeks after transplantation and additionally when clinically indicated. This histopathological diagnosis of rejection was determined by transbronchial biopsy and made according to the working formulation for classifying and grading pulmonary rejection [4]. Briefly, acute cellular rejection was classified into four grades: grade 1, minimal acute rejection; grade 2, mild acute rejection; grade 3, moderate acute rejection; and grade 4, severe acute rejection. Indications for a clinical diagnosis rejection were a change in chest roentgenogram or clinical symptoms such as fever, increased coughing, worsening gas exchange, or a complaint of shortness of breath. Rejection episodes were treated initially with a steroid bolus.

Interleukin 6 Testing

Blood samples were collected daily for 2 to 4 weeks in glass tubes without anticoagulant agents. Serum was obtained immediately after centrifugation at 2,000 rpm for 10 minutes. Aliquots were stored in polypropylene tubes at $-70^\circ C$ until assayed.

Testing for IL-6 was performed by the two-step sandwich enzyme immunoassay method using an ELISA kit (Quantikine Human IL-6; R & D Systems, Inc, Minneapolis, MN). Briefly, 50 μL of assay buffer (buffered protein base) was added to 96-well microplates coated with mouse anti-human IL-6 monoclonal antibodies (first antibody), then 200 μL of serum was aliquoted to microplates. After a 2-hour incubation period at room temperature, the wells were washed and 200 μL of horseradish peroxidase-conjugated goat anti-human IL-6 polyclonal antibody was added. After an additional 2-hour incubation at room temperature, the wells were washed again and incubated at room temperature for 20 minutes with chromogen, a mixture of H_2O_2 and tetra-methylbenzidine. Then 50 μL of 2 N H_2SO_4 was added to stop the reaction, optical density at 450 nm was measured using a microtiter reader (Titertek Multiskan; Flow Laboratories, Inc, McLean, VA), and serum cytokine levels were obtained from the standard curve. Assay sensitivity was 10 pg/mL. More than 70

pg/mL of serum IL-6 was considered abnormal. A spike was considered as an elevation of more than 70 pg/mL from the normal value, which then became normal within 4 days.

Statistics

Statistical analysis was performed by the Welch *t* test. The difference was considered statistically significant when *p* was less than 0.05.

Results

Posttransplantation IL-6 elevation patterns were classified into four groups (schematic configurations are illustrated in Figure 1).

Group 1

In group 1, serum IL-6 remained negative throughout the monitoring period ($n = 1$; 6%). The 1 patient in this category has no significant elevation of serum IL-6 and no infection or rejection episodes during the monitoring period.

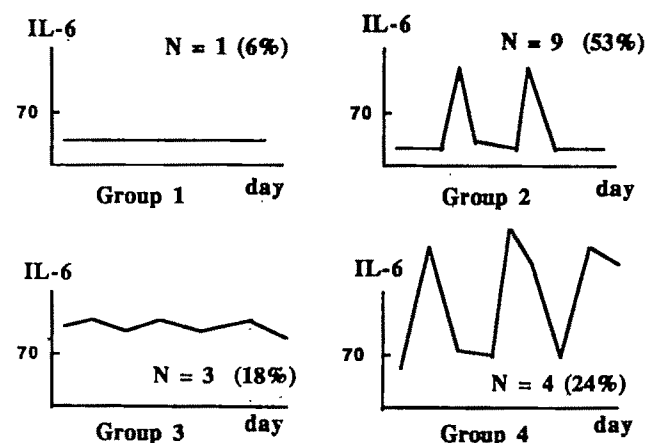


Fig 1. Scheme of interleukin 6 (IL-6) elevation in four groups: group 1, no significant IL-6 elevation; group 2, several spikes with normal baseline; group 3, consistently high serum IL-6 levels; group 4, some spikes with high IL-6 baseline.

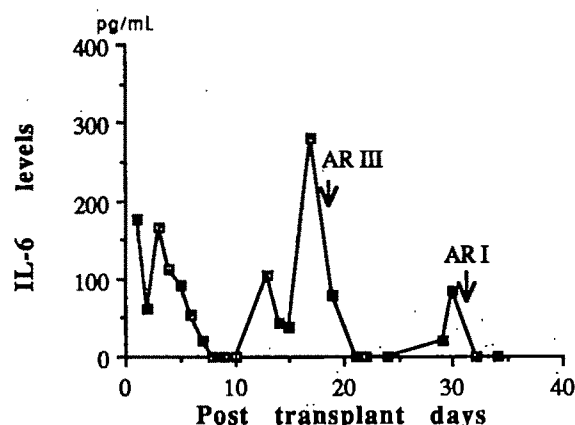


Fig 2. Posttransplantation interleukin 6 (IL-6) monitor pattern of a patient in group 2. (AR I = minimal acute rejection; AR III = moderate acute rejection.)

Group 2

Group 2 consisted of patients with several sharp spikes of IL-6 elevation with normal baseline ($n = 9$; 53%). A total of 19 sharp spikes were observed in the 9 patients in this group, 13 of which (68%) were associated with the presence of rejection episodes. There were 14 histopathologically or clinically diagnosed rejection episodes, 13 of which showed an IL-6 elevation (93%). Interestingly, an elevation of serum IL-6 level was noted 3 days before the histopathological diagnosis in 3 patients and 2 days before diagnosis in another 3 patients. The other 5 serum IL-6 spikes were observed 1 day before diagnosis, and 2 spikes, coincidentally, were observed after the day of rejection diagnosis. In addition, a sharp elevation of serum IL-6 was observed in 4 instances; 3 with acute bronchitis and 1 with diffuse alveolar damage. Two spikes of serum IL-6 level did not correlate with the presence of any significant clinical rejection episodes (biopsy was not performed). The IL-6 monitoring pattern of 1 patient in this group is demonstrated in Figure 2.

Group 3

Posttransplantation serum IL-6 levels remained consistently high in 3 patients (18%); 1 suffered from cytomeg-

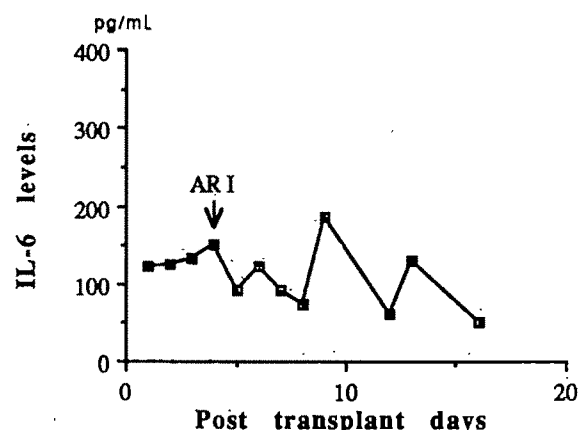


Fig 3. Posttransplantation interleukin 6 (IL-6) monitor pattern of a patient in group 3. (AR I = minimal acute rejection.)

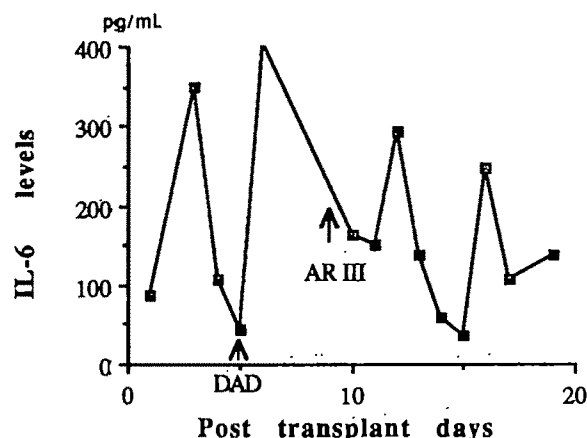


Fig 4. Posttransplantation interleukin 6 (IL-6) monitor pattern of a patient in group 4. (AR III = moderate acute rejection; DAD = diffuse alveolar damage.)

alovirus infection, 1 from toxic megacolon, and 1 from repeated bacterial infections including bronchitis and pneumonia. The posttransplantation IL-6 configuration of the patient who suffered from toxic megacolon is demonstrated in Figure 3.

Group 4

Group 4 patients had several sharp spikes of serum IL-6 elevation with abnormally high IL-6 baseline ($n = 4$; 24%). All 4 patients suffered from severe pneumonia, which resulted in serious posttransplantation complications: 2 received retransplantation, 1 of whom died 21 days after transplantation. The 2 remaining patients who did not receive retransplantation died; 1 at 3 weeks and 1 at 3 months after transplantation. The posttransplantation IL-6 pattern of 1 patient is illustrated in Figure 4.

Results Summary

The postoperative features of the four groups are summarized in Table 2. It should be noted that 3 patients in group 4 died, whereas there were no deaths within 3 months in any of the other groups. In addition, the average intensive care unit stay for patients in groups 3

Table 2. Posttransplantation Statistics According to Serum Interleukin 6 Elevation Pattern

IL-6 Elevation Pattern	Patients	Transplants	Graft Loss	Death*	Average ICU Stay (days)
Group 1	1	1	0	0	4.0
Group 2	9	9	0	0	4.1
Group 3	3	3	0	0	24.2
Group 4	4	6 ^b	5	3	54.0

* Death within 3 months after transplantation. ^b Two patients received retransplantation.

ICU = intensive care unit; IL-6 = interleukin 6.

and 4 was significantly longer than for those in group 1 or 2 ($p < 0.01$).

Comment

Interleukin 6 is produced principally by activated T lymphocytes and macrophages, although some levels of IL-6 are produced by endothelial cells and fibroblasts [10]. The production of IL-6 by T lymphocytes requires the presence of macrophages, whereas macrophages alone can produce IL-6 [11]. T lymphocytes, which require an antigen presentation by macrophages, play a significant role in mediating cellular rejection in lung transplantation [2]. However, IL-6 production by macrophages reaches its peak within a few hours after antigen challenges, whereas it takes 2 days for T lymphocytes to secrete significant levels of IL-6 [11]. In addition, the T lymphocyte activation process requires the presence of IL-6, which is primarily produced by macrophages [12]. Alveolar macrophages play a crucial role in defending the host immune system, particularly in an acute phase of inflammation [13]. Therefore, we assumed that an elevation in serum IL-6 in lung recipients reflects a level of macrophage activation that could be triggered by infection or acute cellular rejection.

This study revealed three primary patterns of IL-6 level elevation in lung transplant recipients: sharp and spike-like, continuous, and a combination of the two. A spike-like IL-6 elevation was associated with presence of histopathologically proven or clinically suspected rejection, whereas a continuous elevation pattern correlated with the presence of infection. A combination of the two patterns indicated the presence of severe pneumonia and a poor prognosis. Thus, posttransplantation IL-6 configuration appears to have an association with clinical outcome for lung transplant patients. However, it should be noted that meticulous posttransplantation IL-6 monitoring is essential in making a differential diagnosis because spike elevation and continuous elevation must be distinguished.

A sharp IL-6 spike could have predictive value in diagnosing an acute cellular rejection. Of 13 IL-6 spikes associated with acute rejection in group 2, a majority were observed before the actual clinical diagnosis of rejection. Three spikes occurred in 3 days, 3 in 2 days, and 5 were 1 day before the actual diagnosis of rejection. There were reports that the other cytokines such as tumor necrosis factor α were produced at the time of cellular rejections in kidney or liver grafts [14, 15] and that soluble IL-2 receptors were clearly detectable during rejection episodes in lung transplant recipients [16]; however, there was no predictive value. Based on our earlier study [10] and the kidney transplant study [17], IL-6 monitoring could be more useful than other cytokine monitoring because the majority of serum IL-6 elevations were detectable before the actual diagnosis of rejection. In fact, messenger RNA of IL-6 was clearly demonstrated in the very early phase of rejection in the rat lung transplant model [18].

Six spikes were observed without the clear presence of

rejection episodes: 3 in conjunction with acute bronchitis, 1 with diffuse alveolar damage, and 2 without significant clinical episodes. If the study were focusing only on diagnosing rejection, these would be false positives. However, it should be noted that four instances of sharp IL-6 elevation reflected macrophage activation. The remaining two spikes could merely be false positive, but there is a possibility that they might reflect subclinical macrophage activation. Interestingly, in 3 patients with acute bronchitis, the presence of infection did not necessarily produce a consistently high level of IL-6, probably because the infections were mild and easily treatable.

The longer intensive care unit stay required for patients with persistent high levels of serum IL-6 must be explained by the fact that they suffered from severe pneumonia with extremely activated alveolar macrophages.

In summary, meticulous monitoring of the posttransplantation configuration of IL-6 levels provides some predictive value in diagnosing rejection or infection in lung transplant recipients.

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Upper Gastrointestinal Dysmotility in Heart-Lung Transplant Recipients

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Recipient pneumonectomy and the necessity for meticulous hemostasis in heart-lung transplantation can result in injury to the vagus nerves as they course through the posterior mediastinum, with consequent delay in gastric emptying. This has been reported to lead to chronic aspiration and associated pulmonary sequelae. To study the association between delayed gastric emptying, bronchiectasis, and bronchiolitis obliterans after heart-lung transplantation, we performed esophageal manometry, 24-hour pH monitoring, and radioisotopic gastric emptying in 10 patients who underwent heart-lung transplantation. Three patients had grossly delayed liquid and solid emptying that was compatible with complete vagotomy. Six other patients had delayed liquid but normal solid emptying—an unexplained finding that is the

reverse of what one would expect from vagal injury. Two of these 9 patients had esophageal dysmotility, but none demonstrated gastroesophageal reflux. One remaining patient had faster than normal gastric emptying for both solids and liquids. Of the 10, 2 patients have radiologic changes of bronchiectasis and 3 have biopsy evidence of obliterative bronchiolitis. There is no relationship between these sequelae and the occurrence of esophageal dysmotility, gastroesophageal reflux, or vagotomy. We conclude that gastric emptying abnormalities can occur after heart-lung transplantation, but such abnormalities are not associated with gastroesophageal reflux and the development of pulmonary sequelae, as previously reported.

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Combined heart-lung transplantation is now an accepted modality of treatment for end-stage pulmonary vascular and selected chronic lung diseases. The importance of preserving the phrenic, vagus, and recurrent laryngeal nerves during recipient cardiopneumectomy was emphasized in the early reports [1, 2]. Nevertheless, postoperative esophageal dysmotility and delayed gastric emptying have been reported [3, 4], and there is speculation that these sequelae may predispose to chronic aspiration and consequent pulmonary sepsis. To further define the nature and effect of vagal denervation in heart-lung recipients, we have studied 10 patients by esophageal manometry, ambulatory 24-hour pH monitoring, and radioisotopic gastric emptying.

Material and Methods

From June 1988 to July 1991, 25 heart-lung transplantations were performed at our institution. The operative technique employed has been reported elsewhere [1]. Seventeen patients are currently alive. All were invited to take part in the study but only 10 gave informed consent. Patient details are given in Table 1.

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Symptomatology was assessed by direct interview with the patients and completion of a standard questionnaire. Aspiration was diagnosed by classic symptomatology, the presence of foreign material during transbronchial biopsy, or both.

Esophageal manometry was performed as previously described [5], using a Gaeltec six-channel esophageal strain-gauge transducer.

Twenty-four-hour pH was monitored with a Synectics Medical 2.1-mm monocrystalline antimony pH catheter introduced nasogastrically and positioned 5 cm above the gastroesophageal junction. Intraluminal pH was recorded by a Synectics Medical Mk 2 Digitrapper at 30-second intervals. Data were downloaded into an IBM PS/2 computer and analyzed by the EsopHogram software package (version 5.50C2; Gastrosoft Inc, TX). Results were expressed in terms of the length and severity of reflux episodes, and whether they were acid or alkaline in nature.

Radioisotopic gastric emptying studies were performed after oral administration of technetium 99m-radiolabeled liquid (12 MBq) and solid (12 MBq) test meals on consecutive days. Patients fasted and then were placed in a standard, reproducible anteroposterior upright position with the large field of view gamma camera centered over the abdomen. The liquid test meal consisted of 150 mL of radiolabeled lactulose solution as a nonabsorbable

Table 1. Details of Heart-Lung Transplant Recipients

Patient No.	Age (y)	Sex	Diagnosis	Survival (mo)	Surgical Complications
1	36.9	F	CHD	40	Gastric outlet obstruction, pyloric dilatation, left vocal cord paralysis
2	36.7	M	PPH	39	...
3	37.8	F	Emphysema	32	...
4	29.9	M	Cystic fibrosis	30	Thoracotomy for bleeding
5	32.5	F	Asthma*	29	Gastric paresis, pyloroplasty
6	26.9	M	Bronchiolitis obliterans	21	...
7	35.9	F	Cystic fibrosis	21	Thoracotomy for bleeding
8	22.7	M	Bronchiectasis	19	Gastric paresis
9	33.4	M	CHD	12	Pseudoobstruction, laparotomy
10	37.5	F	PPH	4	Gastric paresis, pyloroplasty

* With destructive bronchiolitis.

CHD = congenital heart disease; PPH = primary pulmonary hypertension.

marker. A radiolabeled scrambled egg, toast, and tea meal of 400 calories was used for the solid meal. Images were collected into a 64 × 64 computer matrix. Forty sequential images each of 1-minute duration were used for the liquid gastric emptying study. The solid emptying phase was measured at intervals for up to 4 hours after ingestion.

Data analysis used regions of interest drawn around the gastric activity. Time activity curves were derived with correction for radioactive decay. Corrections for radiation attenuation arising from translocation of the meal were not made. The relatively small meal mass and the normal/lean build of the subjects were considered justification for avoiding this potentially cumbersome correction factor [6]. The time activity curves were analyzed to determine the half-emptying time as the simplest measure of dynamic emptying. The measured half-times were compared with the department's established control ranges: liquid phase, 16 to 36 minutes, and solid phase, 110 to 230 minutes. Where half-emptying was not achieved within the control range for liquids, the actual percentage emptied at 36 minutes was determined.

Chest roentgenograms and transbronchial biopsies were independently reported by a radiologist and pathologist, respectively. Transbronchial biopsy is performed either on clinical indication or routinely on postoperative days 7 and 28 and at 3-monthly intervals thereafter. Hence, all patients were studied within 3 months of their last biopsy. Bronchiectasis was defined as the presence of increased lung markings, "tramlining," cystic changes, and associated collapse, fibrosis, or consolidation on the chest roentgenogram [7] or computed tomographic scan.

Results

Flatulence (7/10), nausea (7/10), and gastroesophageal reflux (6/10) were common early postoperative symptoms, which necessitated treatment with prokinetic agents in 5 patients, with clinical improvement. By contrast, aspiration (3/10), chronic cough (4/10), dysphagia (3/10), and heartburn (0/10) were less common.

Three patients had grossly delayed liquid and solid

emptying on radioisotopic gastric emptying that was compatible with complete vagotomy. Of the 3, 1 demonstrated uncoordinated esophageal contractions and failure of relaxation of the lower esophageal sphincter on barium swallow, and none had gastroesophageal reflux on 24-hour pH monitoring (Table 2). All 3 patients complained of dysphagia in the early postoperative period, but none suffered from aspiration or chronic cough. Postprandial nausea, flatulence, bloating, and vomiting were frequent symptoms: 2 patients required pyloroplasty for relief whereas symptoms resolved with prokinetic agents and the passage of time in the third.

The 7 remaining patients had no evidence of vagal injury on radioisotopic gastric emptying: 6 had delayed liquid but normal solid emptying—an unexplained finding, which is most unusual and the reverse of what one would expect with vagotomy. One had faster than normal gastric emptying (see Table 2). Esophageal manometry demonstrated lower two-thirds dysmotility in 1 of these patients (patient 7), and 24-hour pH monitoring showed significant gastroesophageal reflux in another (patient 4). One patient (patient 1) exhibited clinical gastric outlet obstruction postoperatively and required balloon dilation of the pylorus; this patient had intraoperative trauma to her left recurrent laryngeal nerve and presumably had concomitant vagal damage that has since recovered. Another (patient 9) underwent a negative laparotomy postoperatively for pseudoobstruction, without any apparent predisposing factors.

Of the 10 patients, 2 have radiologic changes of bronchiectasis and 3 have biopsy evidence of obliterative bronchiolitis (see Table 2). There is no obvious relationship between these sequelae and the occurrence of esophageal dysmotility, gastroesophageal reflux, or vagotomy.

Comment

Recipient pneumonectomy and the necessity for meticulous hemostasis in the posterior mediastinum during heart-lung transplantation places the vagus nerves at risk of injury, either by direct trauma or by thermal injury

Table 2. Results of Investigations

Patient No.	Esophageal Manometry	24-Hour pH DeMeester score ^a	Gastric Emptying		Bronchiectasis	Obliterative Bronchiolitis
			Liquid ^b	Solid (min) ^c		
1	Normal	15.7	20%	132	No	No
2	Normal	4.4	20%	200	No	No
3	Normal	15.4	23%	110	Yes ^d	Yes
4	Normal	86.4	61%	61	No	No
5	Normal	10.6	28%	>>230	No	No
6	Normal	12.9	14%	120	No	No
7	Poor peristalsis	38.8	24%	134	Yes ^d	Yes
8	Failed intubation	9.1	23%	>>230	No	Yes
9	Normal	21.9	41%	150	No	No
10	Uncoordinated ^e	Refused	10%	>>230	No	No

^a DeMeester reflux score; normal <50. time (normal, 110 to 230 minutes).

^b Values represent percentage emptying at 36 minutes (normal, >50%).

^d Postpneumonic.

^e On barium swallow.

^c Values represent half emptying

from electrocautery. Anatomic considerations suggest that the vagi are most likely to be injured at or near the lung hila. Thus both nerves pass posteroinferiorly in the mediastinum to reach the posterior surface of the corresponding lung root; the right nerve in direct apposition to the trachea, the left in the interval between the common carotid and subclavian arteries initially and then on the left side of the aortic arch, posterior to the phrenic nerve. At the lung root each nerve gives branches to the pulmonary plexuses and then divides into two or more branches that pass inferomedially to unite with the corresponding branches of the opposite vagus to form a plexus surrounding and supplying the esophagus [8]. Complete vagotomy during heart-lung transplantation is therefore only possible at or above the lung roots, before the division of the vagi, and most likely just above the level of the carina, where the recipient trachea is transected.

It is known from the early days of peptic ulcer surgery that complete vagotomy results in prolonged gastric atonia [9], hence the need for drainage procedures. Three of our patients were found on radioisotopic gastric emptying studies to have profound gastric paresis compatible with complete vagotomy, 2 of whom required a drainage procedure for the relief of symptoms.

Six of the remaining 7 patients demonstrated a curious pattern of delayed liquid but normal solid gastric emptying that is incompatible with complete or partial vagotomy. Classically, partial vagotomy results in enhanced liquid but delayed solid emptying. By disrupting receptive relaxation, vagotomy raises intragastric pressure and causes more rapid emptying of liquids, which is dependent on the pressure gradient between the stomach and the duodenum. By disturbing antral motility, solid emptying is retarded [10, 11]. The combination of delayed liquid but normal solid gastric emptying has been reported in elderly subjects [12]; its mechanism and significance in our patients is unexplained.

The physiologic consequences of vagotomy at the carinal level on esophageal function may be inferred from animal experiments. It is well established that the function of the striated esophagus is completely dependent on

its vagal supply, whereas that of the smooth muscle part is largely dependent on its intrinsic neural plexus [13]. At the carinal level, the esophagus is composed of a varying proportion of striated and smooth muscle [14], and the effect of vagotomy is presumably dependent on the amount of striated muscle present. It is interesting that the only patients in this series who complained of dysphagia in the early postoperative period were the 3 who had evidence of complete vagotomy. Of the 3, only 1 (patient 10) has objective evidence of esophageal dysmotility. One other patient (patient 7) has asymptomatic esophageal dysmotility but no evidence of vagotomy; this is perhaps a coincidental finding.

The tone of the lower esophageal sphincter is partly due to myogenic properties and partly due to neural and hormonal influences. Vagotomy in dogs and cats affects lower esophageal sphincter function variably and may lead to decreased resting tone or spasm [13]. Some evidence exists to suggest that delayed gastric emptying in humans may predispose to gastroesophageal reflux [15, 16], although data from vagotomized animals and other clinical studies are conflicting [10, 17-19]. Twenty-four-hour pH monitoring showed no evidence of gastroesophageal reflux in any of our patients with evidence of vagotomy or delayed gastric emptying; ironically, 1 patient with normal gastric emptying had free gastroesophageal reflux, but this is, again, perhaps a coincidental finding.

Our results conflict with those reported by Reid and associates [4], who reported a high incidence of chronic cough and delayed gastric emptying, esophageal dysmotility, or both in their patients. This was associated with evidence of aspiration and bronchiectasis. Five patients in our series reported chronic cough and aspiration as symptoms, none of whom have radiological changes of bronchiectasis. Of the 3 patients with gastric paresis, 2 did not have substantiated gastroesophageal reflux (1 refused pH monitoring), and none have bronchiectasis (see Table 2). The 2 patients who do have bronchiectasis in our series have both had life-threatening postoperative suppurative pneumonia but no evidence of gastroesophageal reflux.

Finally, the only patient who has significant gastroesophageal reflux has no evidence of bronchiectasis. This discrepancy between our observations and those of Reid and associates may partly be explained by the fact that their investigations were performed on a selected group of symptomatic patients. It is also not clear from their report whether "delayed gastric emptying" implied delayed liquid or solid emptying, or both. Furthermore, the diagnosis of delayed gastric emptying in 2 of their patients was based on barium studies, despite normal radioisotopic gastric emptying. Barium estimates of gastric emptying are known to be qualitative at best and misleading at worst [11, 20].

We conclude that there is evidence of esophageal dysmotility and delayed gastric emptying compatible with complete vagotomy in heart-lung recipients; this finding is not correlated with gastroesophageal reflux, chronic aspiration, or the development of bronchiectasis postoperatively. Nevertheless, vagal injury has been a source of early morbidity in these patients, with 3 of our 17 long-term survivors requiring some form of intervention. Modifications to surgical technique that may decrease the risk of vagal injury and improve morbidity include circumpect use of diathermy when securing hemostasis in the posterior mediastinum, and the stapling technique of Vouhe and Darteville [21], in which dissection of the posterior mediastinum is limited. The risk of vagal injury may also be minimized in the alternative operation of bilateral sequential lung transplantation for patients with septic lung disease, in which dissection of the distal trachea, subcarinal region, and posterior mediastinum is avoided [22].

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Surgical Management of Thrombotic Disc Valve

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Thrombotic obstruction, a rare but often fatal complication of cardiac valve prostheses, appears to occur more frequently in tilting-disc valves than in other valve designs. Its diagnosis and surgical treatment remain a challenge. Ten consecutive patients who had thrombosis of a tilting-disc valve prosthesis were treated in Chang Gung Memorial Hospital from November 1982 to August 1990. Preoperative clinical features, including exertional dyspnea, new murmur, and absence of a metallic click from the prosthetic valve, occurred in all of the patients. Symptoms were present for 1 week or more before reoperation in 70% of the patients; nevertheless, many patients were referred only after acute exacerbation of heart failure and development of pulmonary edema. Echocardiography confirmed prosthetic valve malfunction in 90% of the patients. One unconfirmed case was

later documented by cardiac catheterization. Anticoagulant therapy was in the therapeutic range for only half of the patients at the time of admission. Prompt reoperation was performed for thrombectomy (8 patients, all survived) or valve replacement (2 patients, one death). Long-term outcome was satisfactory in all survivors with a mean follow-up of 31.6 months. These findings emphasize the importance of considering the diagnosis of thrombosis in patients with mechanical heart valve prostheses who are first seen with nonspecific symptoms and minor changes of their physical findings. The diagnosis could be easily made by echocardiography. Thrombectomy is an easy, fast, and safe procedure, especially for these critically ill patients.

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Thrombotic obstruction is a rare but often fatal complication of cardiac valve prostheses. This kind of complication occurs more frequently in tilting-disc valves than in other kinds of prostheses [1-15]. Björk and Henze [16] reported that sudden thrombosis in the absence of anticoagulation occurs at the rate of about 3% per year. Even with anticoagulation, 1% of patients with a tilting-disc valve in the mitral position may have this complication. Karp and associates [12] reported the cumulative (actuarial estimate) risks for thrombosis of tilting-disc valves to be 3%, 13%, and 13% at 5 years after aortic, mitral, and combined aortic and mitral valve replacement, respectively; overall incidence was 8.6%.

Surgical treatment of disc valve thrombosis includes both thrombectomy and replacement of the prosthetic valve [9, 17-20]. In this report, we describe the entire series of reoperations for thrombotic obstruction of prosthetic tilting-disc valves at this hospital.

Material and Methods

We retrospectively reviewed the clinical records of all patients who sustained thrombus formation on prosthetic tilting-disc valves and underwent reoperation for malfunctioning disc valves at the Chang Gung Memorial Hospital. Data from 10 consecutive patients from November 1982 to August 1990 were collected.

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Results

Clinical data on the 10 patients are summarized in Table 1. All patients had initial valve replacement at Chang Gung Memorial Hospital. Thrombotic obstruction of the prosthetic valve occurred in the aortic position in 6 patients and in the mitral position in 4 patients. Nine patients had Björk-Shiley tilting-disc valves (five aortic, four mitral), whereas the remaining patient had a Sorin valve (aortic).

The interval between implantation and dysfunction of the disc valve ranged from 2 to 121 months (mean, 43 months). At admission, systemic anticoagulation with warfarin sodium seemed to be adequate (prothrombin time ≥ 1.5 and 2.0 times control in aortic and mitral prostheses, respectively) in 5 of the 10 patients at the time of diagnosis of disc valve thrombosis. However, warfarin had been discontinued occasionally in these 5 patients. In the remaining patients, warfarin was discontinued or used only intermittently. In these patients, the prothrombin time was nearly normal when the symptoms of congestive heart failure developed. None of the patients took antiplatelet agents in our series.

Prominent preoperative symptoms included dyspnea in all 10 patients and angina in 3 patients. Furthermore, 1 patient had had a recent transient neurological deficit and a seizure attack.

The duration of progressing cardiac symptoms before reoperation varied widely: less than 1 week, 3 patients; 1 week to 1 month, 4 patients; 1 to 6 months, 1 patient; and more than 6 months, 2 patients. At the time of the operation, the New York Heart Association classifications

Table 1. Summary of Clinical Data on Patients Undergoing Reoperation for Thrombosed Prosthetic Disc Valve

Patient No.	Age (y)	Sex	Valve Site	Valve Type	Anticoagulation	Interval* (mo)	Reoperation	Outcome
1	35	F	Aortic	B-S	Inadequate	23	Replacement 23-mm C-E	Alive
2	59	F	Aortic	B-S	Adequate	16	Thrombectomy	Alive
3	52	F	Aortic	B-S	Adequate	63	Thrombectomy	Alive
4	55	F	Mitral	B-S	Adequate	2	Replacement 29-mm C-E	Died
5	50	F	Mitral	B-S	Adequate	10	Thrombectomy	Alive
6	48	F	Aortic	B-S	Adequate	85	Thrombectomy	Alive
7	64	F	Aortic	B-S	Inadequate	84	Thrombectomy	Alive
8	65	M	Mitral	B-S	Inadequate	20	Thrombectomy	Alive
9	21	F	Mitral	B-S	Inadequate	121	Thrombectomy	Alive
10	69	F	Aortic	Sorin	Inadequate	5	Thrombectomy	Alive

* Interval from insertion to thrombosis.

B-S = Björk-Shiley; C-E = Carpentier-Edwards.

were class IV for 6 patients, class III for 3 patients, and class II for 1 patient.

Three patients were in cardiogenic shock at the time of valve reoperation. However, these 3 patients, as well as the other symptomatic patient, had milder symptoms for periods ranging from 2 days to 1 year preoperatively. These minor symptoms were initially diagnosed as a flu-like illness, chronic obstructive lung disease, or mild congestive heart failure due to progressive left ventricular dysfunction.

The diagnosis of prosthetic valve malfunction was suspected from clinical examination and various laboratory evaluations. A new murmur developed in all 10 patients, in whom a decrease to absence of the metallic click of the prosthetic valve was also detected. Other physical findings included hypotension in 4 patients, 3 of whom were in overt cardiogenic shock. In addition, 1 patient denied serious cardiac limitation but was noted to have severe hemolytic anemia at the time of routine follow-up. The results of the physical examination, however, suggested valve malfunction.

Diagnostic studies included chest roentgenography, the results of which were abnormal in all 10 patients. Abnormal findings were pulmonary venous congestion or cardiomegaly. Fluoroscopy with cineradiography, an important and noninvasive diagnostic tool, was not available for analysis because the results were not formally recorded. Furthermore, echocardiograms were obtained from all 10 patients. Nine patients were thought to have findings indicative of prosthetic valve dysfunction, and reoperations were scheduled without further diagnostic delay. These positive findings included restricted disc excursion with decreased opening and closing rates, increased echodensity over the prosthetic valve, and abnormally high transvalvular pressure gradient and maximal velocity. For the only patient with unconfirmed diagnosis, cardiac catheterization was performed, and prosthetic valve dysfunction was confirmed by documentation of valvular incompetence and delineation of disc mobility.

The timing of reoperation depended on the time necessary for establishing the correct diagnosis of thrombotic

obstruction of the prosthetic valve. The period from hospital admission to operation was more than 1 day for 8 patients, and only 2 patients underwent operation within 24 hours. However, emergency operations were performed in all patients once the diagnosis was established. Simple thrombectomy without valve replacement was performed on 8 patients under cardiopulmonary bypass. The thrombotic prostheses were approached from both sides through a left atriotomy and aortotomy. The thrombotic material was removed manually using angled forceps and open-tipped suction [17]. The disc mechanism was rotated to clear all quadrants (except in patient 10, whose prosthesis was unrotatable). A laryngeal mirror was also employed to ensure that all the thrombus was cleaned off. The disc mechanism was found to be free from any mechanical impairment. At termination of this procedure the disc mechanism was aligned so that the disc had free motion. The other 2 patients (patients 1 and 4) received valve replacement with a Carpentier-Edwards prosthesis due to poor compliance with the warfarin regimen and the preference of the patients. The aortic cross-clamp time was significantly different between the replacement group (51 ± 4 minutes) (mean $\pm$ standard error of the mean) and the thrombectomy group (31 ± 2 minutes) ($p < 0.01$).

All but 1 of the patients had an uncomplicated postoperative course and was discharged uneventfully. The only hospital death occurred in a patient (patient 4) who sustained persistent low cardiac output despite replacement of the obstructed valve.

All the survivors were closely followed up; follow-up time ranged from 5 to 101 months with a mean of 31.6 months. There were no late thromboembolic episodes during the follow-up period. Excellent prosthetic valve function was demonstrated by echocardiographic studies. All patients were in New York Heart Association class I or II. Anticoagulant (warfarin sodium) was prescribed to patients receiving thrombectomy. Prothrombin time was maintained from 1.5 to 2.0 or 2.0 to 2.5 times control for aortic or mitral prostheses, respectively.

Comment

The reported incidence of Björk-Shiley valve thrombosis ranges from 1% to 8% [1-15]. Reports have emphasized the sudden, precipitous deterioration in hemodynamics and high mortality after reoperation in these critically ill patients [21]. However, Kontos and colleagues [22] found that nonspecific symptoms were present for 1 week or more before reoperation in 86% of their patients. In this review the chronicity of the symptoms before presentation was also elucidated. Seventy percent of the patients had clinical evidence of valve dysfunction for 1 week or more before reoperation; many of these patients had acute deterioration just before hospital admission. These results are especially pertinent for physicians who are responsible for the follow-up of patients with prosthetic valves. Relatively minor symptoms, especially pulmonary congestion, should prompt a careful cardiac examination to exclude the possibility of prosthetic valve thrombosis. Change to absence of the prosthesis-related metallic click was the most significant finding. Other nonspecific clinical findings include systolic and diastolic murmurs and hemolytic anemia.

Echocardiography combined with Doppler studies remained the first-line diagnostic procedure for documentation of prosthetic valve thrombosis in this institute because of its convenience and noninvasiveness. All 10 patients received this examination soon after admission, and high accuracy was exhibited, with 9 of the 10 patients showing positive findings indicating valve dysfunction. Although fluoroscopy with cineradiography in two simultaneous planes has been shown to increase the accuracy of detecting disc valve dysfunction [23], an unacceptably high false-negative rate of 64% was still noted in the Kontos series [22]. This fluoroscopy technique was not routinely used in our series. Cardiac catheterization, despite continuing to be the most sensitive diagnostic procedure in the evaluation of a patient who is suspected of having prosthetic valve thrombosis [9], was reserved for the patient with unconfirmed diagnosis by echocardiography because of its invasiveness and even danger to these hemodynamically crippled patients.

Inadequate systemic anticoagulation had been reported to be the main cause of the thrombosis [19, 24]. In our and Kontos' series [22], however, half of the patients were documented to have had adequate anticoagulation at the time of admission. Nevertheless, occasional discontinuation of anticoagulant therapy at some time in the patient's history were noted and this might have been associated with a rebound hypercoagulable state, which has been reported to result in an increased rate of thromboembolic complications [25].

Surgical treatment of disc valve thrombosis includes both thrombectomy and replacement of the prosthetic valve [9, 17-20]. Thrombectomy was considered to be the procedure of choice in our series because of its ease and rapidity—that is, it is a safe procedure in these critical conditions. The thrombus could be easily removed from both sides of the valve through a left atriotomy and aortotomy.

In contrast to the reported mortality from prosthetic valve thrombosis ranging from 33% to 100% [3, 5, 7-9, 11, 12], a mortality rate of 10% was noted in this series. We would like to stress the importance of close observation of any patient with a mechanical heart valve, especially a tilting-disc prosthesis, who is seen with nonspecific cardiac symptoms. A thorough evaluation to rule out the possibility of thrombotic obstruction of the prosthesis should be performed. For most patients, early reoperation will give the best results. Thrombectomy is an easy, fast, and safe procedure for these critical patients. In patients who are in stable condition preoperatively, operative mortality is low.

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Improved Recovery of Immature Myocardium With L-Glutamate Blood Cardioplegia

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Enhancement of myocardial recovery with glutamate-enriched cold blood potassium cardioplegia (BPC) was evaluated using an isolated working heart model. Three groups of hearts from immature rabbits were subjected to 20 minutes of warm (37°C) ischemia to allow energy depletion, followed by 90 minutes of hypothermic (10°C) ischemia. Myocardial protection provided during hypothermia consisted of cardioplegia infusion, at 50 mm Hg every 30 minutes at 4°C, of either St. Thomas' Hospital solution (group 1, $n = 6$), oxygenated BPC (group 2, $n = 7$), or oxygenated BPC enriched with 20 mmol/L L-glutamate (group 3, $n = 7$). Percent recovery of aortic flow was $87.6\% \pm 6.3\%$ (results expressed as mean $\pm$ standard error of the mean) in group 3, which was significantly

better than for either group 1 ($63.4\% \pm 4.0\%$) or group 2 ($47.0\% \pm 3.5\%$) ($p < 0.05$ by analysis of variance). Group 3 hearts had significantly better recovery of myocardial energy stores ($\mu\text{mol/g}$ dry weight) compared with group 1 or 2 hearts: adenosine triphosphate, 17.8 ± 1.1 versus 12.4 ± 1.5 and 12.1 ± 0.4 ; creatine phosphate, 25.9 ± 1.8 versus 17.8 ± 1.8 and 20.3 ± 0.7 ; and glycogen, 140.7 ± 12.6 versus 98.7 ± 9.9 and 60.7 ± 9.9 ($p < 0.05$). Glutamate-enriched BPC provided excellent myocardial protection after ischemia in this immature model, and this study quantitatively supports the use of glutamate-enriched BPC in neonatal clinical practice.

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In an effort to improve myocardial function after cardiac operations, much research has centered on optimizing cardioplegic solutions. Cold blood potassium cardioplegia with a normal calcium concentration together with topical hypothermia has been shown to offer superior protection over crystalloid cardioplegia and hypothermia [1], probably because blood cardioplegia delivers a superior buffering capacity provided by the histidine portion of the hemoglobin molecule. Evaluation of the myocardial protective properties of amino acids, particularly glutamate, in cardioplegic solutions stemmed from investigations into the source of anaerobic energy production in the musculature of diving mammals [2]. Postulated biochemical pathways utilizing Krebs cycle intermediate compounds including glutamate and aspartate were established, allowing for anaerobic production of energy and maintenance of the cellular redox potential.

Rosenkranz and associates [3] found that glutamate-enriched blood cardioplegia improved myocardial recovery in an adult canine model. However, neonatal myocardium responds differently to ischemia than does adult myocardium due to differences in structure, function, and metabolism [4]. Therefore, experience gained with myocardial preservation in the adult cannot automatically be

applied to the neonate. The goal of this study was to determine the effect of glutamate enrichment to blood cardioplegia on the functional and metabolic recovery of immature energy-depleted myocardium.

Material and Methods

Hearts from immature (3 to 4 weeks; mean weight, 521 g; range, 467 to 590 g) rabbits were studied. Anesthesia was induced with 4% halothane. Heparin (500 mg/kg), pentobarbital (30 mg/kg), and pancuronium bromide (0.1 mg/kg) were given intravenously. Each heart was excised and weighed. The aorta was cannulated and then connected to the isolated working heart apparatus with retrograde aortic (Langendorff) perfusion initiated from a reservoir 60 cm above the heart. The pulmonary veins were ligated, excess mediastinal tissue was trimmed, and the left atrium was cannulated for conversion to the working heart model. All animals received humane care in compliance with the Society for Medical Research and the Guide for the Care and Use of Laboratory Animals prepared by the National Academy of Sciences and published by the National Institutes of Health (NIH publication No. 85-23, revised 1985).

Working Heart Model

An isolated working heart model was used, as described by Neely and associates [5]. To begin the working heart mode, Langendorff perfusion was stopped and the left atrium was filled with oxygenated Krebs-Henseleit buffer. The heart ejected the fluid through the aortic cannula into a chamber with an adjustable resistance to flow. The

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aortic pressure can be raised by increasing the resistance to flow; therefore, aortic flow and mean aortic pressure are inversely related.

The coronary arteries were perfused by the cardiac output generated by the left ventricle. Coronary return was ejected from the right ventricle and collected and recirculated with the aortic flow. Left atrial pressure was adjusted by altering the height of the left atrial reservoir. To induce ischemia, the left atrial perfusion was stopped and the aortic outflow channel was clamped. Cardioplegic solution was infused into the aortic root through a separate cannula.

The Langendorff perfusate consisted of a modified Krebs-Henseleit buffer equilibrated with 95% oxygen and 5% carbon dioxide, with a pH of 7.4 at 37°C. The composition (in mmol/L) of the buffer was as follows: NaCl, 118; KCl, 4.7; CaCl₂, 2.5; MgSO₄, 1.2; KH₂PO₄, 1.2; Na₂EDTA, 0.5; NaHCO₃, 25; and glucose, 11.1. The working solution was identical, with the exception of the addition of insulin (2.5 U/L) and bovine serum albumin (to a final concentration of 0.2%). Oxygen tension in both the Langendorff and working perfusates ranged from 475 to 525 mm Hg.

Experimental Sequence

After the heart was mounted on the aortic cannula, the following sequence was followed: 10 minutes of Langendorff perfusion; a 15-minute working period; 20 minutes of warm (37°C) ischemia (to produce energy depletion); 90 minutes of hypothermic (10°C) ischemia; 10 minutes of Langendorff reperfusion; and a second 15-minute working period.

Myocardial Preservation

Three methods of myocardial preservation were evaluated during the 90-minute period of hypothermia: in group 1, 6 hearts received a 10-mL/kg body weight infusion of St. Thomas' Hospital crystalloid cardioplegia (Plegisol; Abbott Laboratories, Chicago, IL) at 4°C every 30 minutes at 50 mm Hg; in group 2, 7 hearts received an infusion of oxygenated blood potassium cardioplegia at 4°C for 2 minutes at 50 mm Hg every 30 minutes; and in group 3, 7 hearts received an infusion of oxygenated blood potassium cardioplegia enriched with 20 mmol/L of L-glutamate (monosodium glutamate) also at 4°C for 2 minutes at 50 mm Hg every 30 minutes. With each method, myocardial temperature was maintained at 10°C by immersion in a cold saline bath. The cardioplegia was delivered according to the current clinically used methods, crystalloid cardioplegia based on weight of patient, blood cardioplegia based on timed delivery.

The blood cardioplegia was prepared by mixing an initial solution to blood (obtained from adult rabbit donors) in a ratio of 1:4. The initial solution contained per liter: 10 g of glucose, 3.6 g of KCl, 1.2 g of NaCl, 5.0 g of Tris-buffer, 2 mL of 3% papavarine, and 20 U of insulin. The basic indices of the blood cardioplegia were 16 mEq K⁺/L, 100 mEq Na⁺/L, pH of 7.8 (37°C), osmolality of 330 mOsm/L, hematocrit of 0.25, and temperature of 9°C. The blood cardioplegia was continuously circulated, filtered with a 40-μm Pall blood transfusion filter (Pall Biomedical

Inc, Fajardo, PR), and oxygenated using a Sarns Pediatric Membrane Oxygenator (Sarns Inc/3M, Ann Arbor, MI) to an oxygen tension of 200 to 300 mm Hg. The crystalloid cardioplegia was unoxygenated and filtered through a 0.45-μm filter.

Measurement of Myocardial Preservation

Aortic flow was measured by timed collections from the aortic ejection line. Systolic, diastolic, mean aortic, and left atrial pressures were continuously measured with a disposable transducer and recorded on a Siemens System Sirecust 400 monitor. Heart rate was determined by a timed count. The hemodynamic parameters measured during the second working period were compared with those obtained during the first working period. The results were expressed as the percent recovery of the preischemic value.

After completion of the second working period, the hearts were frozen with tongs precooled in liquid nitrogen for later determination of myocardial high-energy phosphate stores. To obtain baseline and energy-depleted values, 6 additional hearts were frozen after the first working period and 6 more after the warm ischemic period. The samples were then stored in a liquid nitrogen tank (-196°C) until assays for adenosine triphosphate (ATP), creatine phosphate, and glycogen, using standard enzymatic spectrophotometer procedures, were performed.

Statistical Analysis

Data are reported as mean ± standard error of the mean. One-way analysis of variance was used to determine statistical differences in hemodynamic performance or myocardial energy stores between groups 1, 2, and 3. When a significant *F* value was identified by analysis of variance, *t* tests modified by the Student-Newman-Keul technique were performed to distinguish differences between the means.

Results

Hemodynamics

Baseline hemodynamic values are presented in Table 1. There were no significant differences among the groups of rabbit hearts before ischemia.

The percent recovery of hemodynamics after ischemia is presented in Table 2. The hearts preserved with glutamate-enriched blood potassium cardioplegia (group 3) had excellent preservation of hemodynamics when compared with the hearts preserved with crystalloid cardioplegia (group 1) or unenriched blood potassium cardioplegia (group 2). The percent recovery of aortic flow, which is the major determinant of functional recovery using this model, was significantly better for group 3 hearts than for either group 1 or 2 hearts. Group 3 enriched hearts also performed significantly better than group 2 unenriched hearts with regard to recovery of systolic aortic pressure, heart rate, and coronary sinus flow. Group 1 hearts had significantly better recovery of aortic flow, systolic aortic pressure, and coronary sinus

Table 1. Preischemic Hemodynamic Values^a

Group	SAP (mm Hg)	MAP (mm Hg)	HR (beats/min)	AF (mL/min)	CSF (mL/min)
1	78.7 ± 1.6	50.8 ± 0.9	168.7 ± 12.0	75.7 ± 6.7	26.7 ± 3.0
2	82.1 ± 1.8	51.1 ± 1.5	173.7 ± 7.8	87.7 ± 8.9	23.7 ± 4.5
3	80.0 ± 2.3	50.0 ± 0.5	146.3 ± 12.0	68.3 ± 7.5	29.7 ± 2.7

^a There were no significant differences between the three groups.

AF = aortic flow; CSF = coronary sinus flow; HR = heart rate; MAP = mean aortic pressure; SAP = systolic aortic pressure.

flow than group 2 hearts. The amount of St. Thomas' Hospital cardioplegia delivered averaged 15 mL for group 1, in contrast to 30.9 ± 4.9 mL in the unenriched blood cardioplegia group 2 and 39.2 ± 1.1 mL in the glutamate-enriched blood cardioplegia group 3. There was no significant difference between the amount of cardioplegia delivered for group 2 and group 3.

Biochemical Preservation

Baseline, warm ischemia, and final myocardial energy stores are presented in Table 3. As expected, all three energy stores decreased after the 20-minute period of warm ischemia. However, this decrease was only significant for measurements of ATP (13.6 ± 1.3 versus 17.8 ± 0.9 $\mu\text{mol/g}$ dry weight). Group 1 and 2 hearts at the completion of the study failed to exhibit any improvement in ATP or creatine phosphate stores with further depletion of their glycogen stores to a significantly lower level when compared with baseline. Group 3 hearts had significantly higher levels of all three energy stores when compared with group 1 and 2 hearts and were comparable to baseline values.

Comment

The importance of providing optimal myocardial protection during pediatric cardiac operations has become evident from clinical studies in which up to 50% of the surgical mortality was due to inadequate myocardial protection [6]. Although topical hypothermia has been shown to offer excellent preservation of the immature heart [7], it is difficult to ensure continuous, global hypothermia during an operation in which the heart must be manipulated. Therefore, cardioplegic solutions, which have been shown to be effective in adults undergoing cardiac operations [8], have been adopted in many centers for use in pediatric cardiac operations. However, most of these solutions were developed in the laboratory using

mature animal models, and recent investigations of their effectiveness in immature models have found them to be inadequate or even detrimental [7]. Experience gained with cardioplegic protection in the adult cannot, therefore, be automatically assumed to pertain to the neonate.

The results of this study indicate that glutamate supplementation to blood cardioplegia offers excellent functional recovery of the energy-depleted immature myocardium and are in agreement with the findings of Rosenkranz and associates [3] who reported its benefit in energy-depleted adult myocardium. Group 3 glutamate-enriched blood potassium cardioplegia-protected hearts performed 24% better than group 1 crystalloid-protected hearts and 41% better than group 2 unenriched blood potassium cardioplegia-protected hearts.

The proposed mechanism whereby glutamate improves the tolerance of these energy-depleted hearts is the enhancement of glycolytic metabolism during ischemia and the improvement of oxidative metabolism after ischemia [3]. Penny and Cascarano [9], however, demonstrated that glutamate enrichment to anaerobically perfused isolated rat hearts can actually stimulate glycogenesis because there was net glycogen synthesis from control values. Our study supports Penny and Cascarano's results, with group 3 hearts containing glycogen levels that were higher than those after the warm ischemic period and that were not significantly different from baseline values. In addition to performing glycogenesis, group 3 hearts were able to replenish their high-energy phosphate stores of ATP and creatine phosphate to baseline levels. In adult energy-depleted hearts, Rosenkranz and associates [3] found glutamate to improve recovery; however, this was accompanied by depletion of ATP stores. Our study suggests that immature hearts may be more resistant to depletion of the adenine nucleotide pool with glutamate enhancement, allowing regeneration of ATP stores during reperfusion. This improved ability of the immature heart to conserve or regenerate ATP with glutamate supple-

Table 2. Percent Recovery of Hemodynamics After Ischemia

Group	SAP	MAP	HR	AF	CSF
1	94.0 ± 1.5 ^a	99.4 ± 0.8	105.3 ± 13.1	63.4 ± 4.0 ^a	115.0 ± 15.0 ^a
2	85.6 ± 2.7	97.2 ± 1.8	91.6 ± 2.3	47.0 ± 3.5	70.1 ± 4.9
3	97.3 ± 0.7 ^b	99.4 ± 0.6	110.5 ± 4.9 ^b	87.6 ± 6.3 ^c	107.3 ± 9.5 ^b

^a $p < 0.05$, group 1 versus group 2. ^b $p < 0.05$, group 2 versus group 3. ^c $p < 0.05$, group 3 significantly different from group 1 and group 2.

AF = aortic flow; CSF = coronary sinus flow; HR = heart rate; MAP = mean aortic pressure; SAP = systolic aortic pressure.

Table 3. Myocardial Energy Stores

Condition	ATP ($\mu\text{mol/g}$ dry wt)	CP ($\mu\text{mol/g}$ dry wt)	Glycogen ($\mu\text{mol/g}$ dry wt)
Baseline	17.8 $\pm$ 0.9	22.7 $\pm$ 1.9	160.8 $\pm$ 15.8
Ischemia	13.6 $\pm$ 1.3 ^a	18.4 $\pm$ 2.4	125.1 $\pm$ 12.9
Group 1	12.4 $\pm$ 1.5 ^a	17.8 $\pm$ 1.8	98.7 $\pm$ 9.9 ^a
Group 2	12.1 $\pm$ 0.4 ^a	20.3 $\pm$ 0.7	60.7 $\pm$ 9.9 ^a
Group 3	17.8 $\pm$ 1.1 ^b	25.9 $\pm$ 1.8 ^b	140.7 $\pm$ 12.6 ^b

^a $p < 0.05$, significantly different from baseline. ^b $p < 0.05$, significantly different from group 1 and group 2.

ATP = adenosine triphosphate; CP = creatine phosphate.

mentation is supported by a clinical report by Pisarenko and colleagues [10]. They found that, during surgical correction of tetralogy of Fallot defects, there was preservation and, in some instances, increases in myocardial ATP stores in intraventricular septal biopsy specimens of hearts protected with glutamate-enriched blood cardioplegia and universal decrease in ATP stores in hearts protected with unenriched blood cardioplegia.

The biochemical recovery of group 1 and 2 hearts revealed that their ATP and creatine phosphate stores were maintained at the levels found after warm ischemia, but with further depletion of their glycogen stores. Although other studies failed to find a correlation between energy stores and functional capacity [3, 7], glycogen levels in this study appear to be a good predictor of functional recovery. The improved functional recovery of group 1 hearts over group 2 hearts also contrasts with Corno and associates' [1] results, in which functional recovery was better with blood cardioplegia than with crystalloid cardioplegia. A possible explanation is that our study used blood cardioplegia in a Langendorff isolated working heart preparation. Our blood cardioplegia circuit may need further refinement, but may emphasize even more the improved recovery seen with glutamate enrichment in this age group.

In summary, glutamate enrichment of blood cardioplegia improves both the functional and biochemical recovery of immature energy-depleted myocardium, which may simulate that seen in cyanotic heart disease. We support its use in pediatric cardiac operations, as it should improve the overall myocardial performance of these patients.

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Histological Study of the Internal Mammary Artery With Emphasis on Its Suitability as a Coronary Artery Bypass Graft

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The internal mammary, musculophrenic, and superior epigastric arteries were unilaterally harvested from 11 individuals (aged 49 to 83 years; mean age, 67 years) and were examined histologically at 1-cm intervals. In 2 individuals the media of the entire internal mammary artery was elastic, whereas in the other 9 individuals we observed an alternating histological pattern in the media of the internal mammary artery, that of the proximal and distal segments being elastomuscular and that of the mid segment being elastic. In 4 of the latter 9 individuals the distal 10% to 20% of the media of the internal mammary artery was muscular with rare elastic lamellae. The media of the first 1 to 2 cm of the musculophrenic and superior epigastric arteries was elastomuscular or muscular with rare elastic lamellae, whereas more distally the media was purely muscular. The degree of intimal hyperplasia was significantly greater in arterial segments

with a purely muscular media (25.6%) than in those with elastic (16.7%), elastomuscular (15.3%), and muscular (with rare elastic lamellae) (17.5%) types of media ($p < 0.01$). The mean cross-sectional luminal area of the elastic segment (1.9 mm²) and proximal and distal elastomuscular segments (1.9 and 1.2 mm², respectively) of the internal mammary artery was significantly greater than that of the muscular segments of the musculophrenic artery (0.9 mm²) and the superior epigastric artery (0.7 mm²) ($p < 0.01$). These findings emphasize the ideal suitability of the internal mammary artery as a conduit in coronary artery bypass grafting, based on its low risk of intimal thickening and its matching caliber, contrasting with less favorable properties of the musculophrenic and superior epigastric arteries.

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The properties of the internal mammary artery (IMA) as an almost ideal arterial conduit in myocardial revascularization are determined by its histological structure, which is unique in that it is the only peripheral artery in the human body that is elastic, being composed of an intima that is limited by a well-formed internal elastic lamina and a media that is formed by a network of circularly and longitudinally interlacing elastic lamellae, between which smooth muscle cells are dispersed in a spirally arranged fashion [1]. Superior long-term patency rates of the IMA graft have led to extended use of this conduit for myocardial revascularization, such as bilateral and sequential IMA grafting [2-4]. For these complex grafting schemes longer mammary pedicles are required to reach the posterior coronary circulation. This necessitates distal dissection up to and beyond the epigastric bifurcation, where the histology of the vessel wall, the degree of intimal thickening, and the luminal size may be different. Because these variables may influence the long-term patency of the IMA in aortocoronary bypass grafting, a thorough histological study of this conduit and its

continuation into the musculophrenic artery (MPA) and superior epigastric artery (SEA) with emphasis on these morphologic features is warranted.

Material and Methods

In this study the IMA was unilaterally (5 from the right side and 6 from the left side) obtained at autopsy from 11 unselected individuals, between 49 and 83 years of age (mean age, 67 years), who had died of noncardiac diseases. None of the patients had hypertension or diabetes mellitus. The IMA was harvested from its origin at the anteroinferior aspect of the first part of the subclavian artery, including a segment of 3 to 4 cm of the subclavian artery, to beyond the epigastric bifurcation, which invariably was located within the limits of the fifth to seventh intercostal spaces. The length of the IMA from its origin to the epigastric bifurcation varied from 17 to 22.5 cm (mean $\pm$ standard deviation, 19.5 $\pm$ 2.4 cm). Both terminal branches, ie, the MPA and SEA, were transected as far distal to the epigastric bifurcation as possible, varying from 3 to 6 and from 5 to 8 cm, respectively.

In all cases, the arteries were fixed in a flaccid state in 4% formaldehyde solution during 1 week. In a previous study [1] we have demonstrated that there is no signifi-

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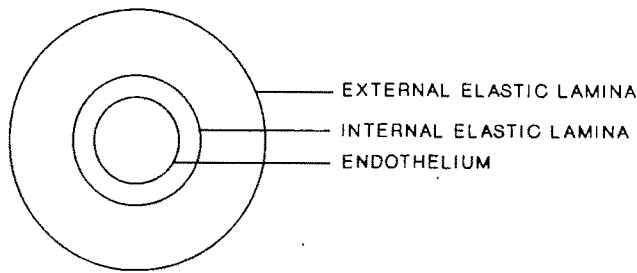


Fig 1. In the internal mammary, musculophrenic, and superior epigastric arteries the perimeters of the endothelium, internal elastic lamina, and external elastic lamina and the respective areas surrounded by these were measured.

cant difference in the width of the intima and media after fixation of muscular or elastic conduits in a flaccid state or at a pressure of 100 mm Hg. Each specimen was laminated in consecutive transverse sections at intervals of 1 cm, starting proximally at the origin of the IMA and ending at the distal segments of the MPA and SEA. Subsequently these sections were embedded in paraffin wax and prepared in 6- μ m sections. Care was taken to ensure that these sections were not oblique and were not adjacent to branching points. All sections were stained with hematoxylin-eosin and elastin-trichrome after Masson techniques.

The morphologic condition of the IMA, MPA, and SEA was studied at the aforementioned consecutive intervals, with emphasis on the histology of the media and the intima. In this scope the number of discontinuities in the internal elastic lamina and the number of elastic lamellae in the media, including the internal and external elastic laminae, were counted. In addition, the degree of presence of smooth muscle cells in the media was estimated in each section.

Subsequently, using a commercially available semiautomatic image analyzing system (MOP-Videoplan; Kontron, Munich, Germany), the perimeters of the endothelial lining (P_{endo}), the internal elastic lamina (P_{iel}), and the external elastic lamina (P_{eel}) were measured (Fig 1). In addition, the cross-sectional areas surrounded by these 3 perimeters (A_{endo} , A_{iel} , and A_{eel} , respectively) were measured. The measurements were carried out with a $\times 2.5$ neofluar objective ($NA = 0.08$). From these measured quantities the following parameters were derived:

1. Mean width of the media according to the formula:
mean width of media = $2 \times (A_{eel} - A_{iel}) / (P_{eel} + P_{iel})$
2. Density of elastic lamellae in the media according to the formula: density elastic lamellae = number of elastic lamellae/mean width of media
3. Degree of intimal hyperplasia according to the formula:
degree of intimal hyperplasia = $(A_{iel} - A_{endo}) / A_{iel} \times 100\%$

Because the IMAs varied considerably in length among the individuals we introduced the concept of relative distance. It is defined as the distance in the IMA distal to the proximal first centimeter (for the explanation of select-

ing this point, see the Morphologic Findings section) with the epigastric bifurcation being the end point, divided by the entire length of the IMA (minus its first centimeter) and multiplied by a factor of 100, which yields the distance percentage.

The differences in the cross-sectional luminal area and the degree of intimal hyperplasia in the three vessels were studied with analysis of variance. The same analysis was performed to investigate the effect of the level in the IMA on cross-sectional luminal area, the number and density of elastic lamellae, and the degree of intimal hyperplasia. Quantitative data with regard to the number of discontinuities in the internal elastic lamina were analyzed with the signed rank test. For multiple comparisons Fisher's least significant difference method was used. A p value less than 0.05 indicates a difference unlikely to be due to chance alone.

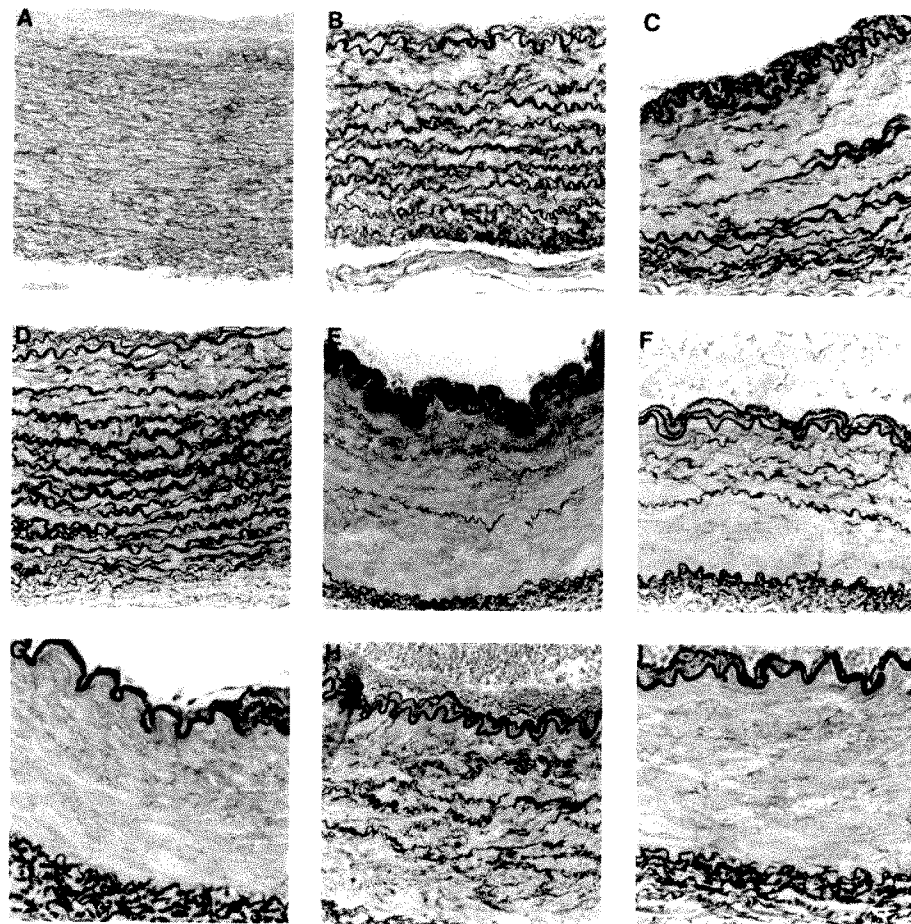
Results

Morphologic Findings

Four histological patterns were defined in the media: (1) the elastic pattern, which contains a minimum of 8 densely packed and concentrically arranged elastic lamellae, including the internal and external elastic laminae, with only moderate presence of smooth muscle cells; (2) the elastomuscular pattern, which contains a minimum of 5 and a maximum of 7 less regularly arranged elastic lamellae, including the internal and external elastic laminae, with abundant presence of smooth muscle cells; (3) the muscular pattern with rare elastic lamellae, which primarily contains smooth muscle cells and 3 or 4 irregularly arranged elastic lamellae, including the internal and external elastic laminae; and (4) the muscular pattern, in which the media consists almost purely of smooth muscle cells with some elastic fibers dispersed in between and without elastic lamellae except the internal and external elastic laminae.

Invariably the subclavian artery was an elastic artery with a media consisting of 30 to 40 elastic lamellae (Fig 2A). In all individuals we observed a varying histological pattern from the proximal IMA to the distal segments of the MPA and the SEA. At the origin of the IMA, in its proximal 1 cm, being a transitional area between the subclavian artery and the IMA, the media invariably was elastic, containing 8 to 18 (mean, 10) elastic lamellae, including the internal and external elastic laminae (Fig 2B). Because of the extremely variable cross-sectional luminal area and intimal thickness in this segment of the IMA it was not further involved in the histological and quantitative analysis. In only 2 individuals, who were 51 and 67 years of age, the media of the IMA was elastic along its entire length, with a number of elastic lamellae that varied from 8 to 12 (mean, 10). In the other 9 individuals we observed an alternating elastomuscular-elastic histological pattern in the IMA: the first 20% to 30% of the total length of the IMA was generally elastomuscular (Fig 2C). In this segment the smooth muscle content in the media prevailed over a number of 5 to 7 (mean, 6)

Fig 2. Documentation of the varying histological pattern of the internal mammary artery (IMA) along its downstream course in a 56-year-old man: (A) Subclavian artery in direct proximity to the origin of the IMA, its media containing 30 to 40 elastic lamellae; (B) The origin of the IMA with a mean number of 10 elastic lamellae in its media; (C) Proximal segment of the IMA with an elastomuscular media, containing a mean number of 5 elastic lamellae; (D) Mid segment of the IMA with an almost purely elastic media containing a mean number of 9 elastic lamellae; (E) Distal segment of the IMA with a predominantly muscular media and a limited number of elastic lamellae; (F) Proximal 1 cm of musculophrenic artery with rare elastic lamellae in a predominantly muscular media; (G) Distal musculophrenic artery with a muscular media containing rare elastic fibers; (H) Proximal 1 cm of superior epigastric artery with few incomplete elastic lamellae in a predominantly muscular media; (I) Distal superior epigastric artery with a muscular media containing rare elastic fibers. (Elastin-trichrome after Masson stain; A: $\times 80$, B to H: $\times 140$, both before 25% reduction.)



elastic lamellae (Figs 3, 4). More downstream in these IMAs we observed a rather abrupt transition into an elastic pattern, which continued up to 70% to 80% of the total length of the IMA. This elastic segment was composed of 8 to 12 (mean, 9) elastic lamellae (Figs 2D, 4, 5). In all 9 individuals we observed a second elastomuscular segment with 5 to 7 (mean, 6) elastic lamellae, analogous to the proximal one, starting at 70% to 80% of the total length of the IMA. In 5 of these 9 individuals this distal elastomuscular segment extended up to the epigastric bifurcation, but in the remaining 4 it abruptly (at 80% to 90% of the total length of the IMA) converted into a muscular one with rare (mean, 3) elastic lamellae (Figs 2E, 3). In all 11 individuals the elastic, elastomuscular, or muscular (with rare elastic lamellae) patterns continued as an elastomuscular or mainly muscular pattern in the media of the first 1 to 2 cm of the MPA, with a mean number of elastic lamellae of 5 and 3, respectively (Figs 2F, 6). In all individuals in the proximal 1 to 2 cm of the SEA only the muscular pattern, primarily without or with incomplete elastic lamellae, was seen (Figs 2H, 7, 8). More distal in the MPA and SEA the media consisted almost purely of smooth muscle cells, with elastic fibers scarcely dispersed in between and without any elastic lamellae (Figs 2G, 2I).

The mean number of discontinuities in the circumfer-

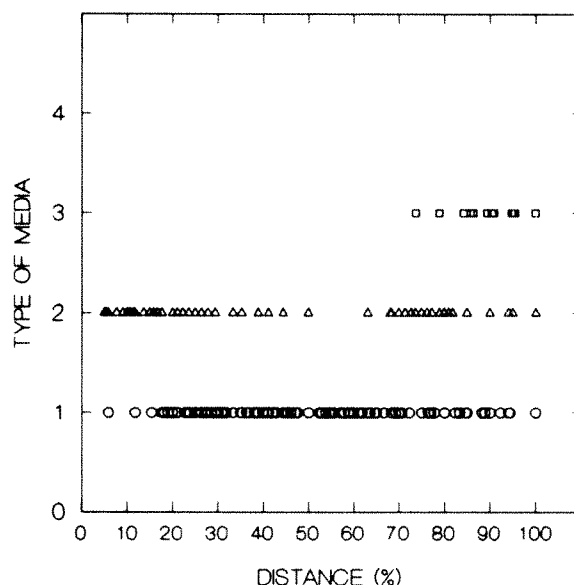


Fig 3. Distribution of the various histological patterns in the media of 11 internal mammary artery specimens. Note the interindividual variability in histological pattern of the media at the various locations. In a minority of patients the media of the distal segment of the internal mammary artery was muscular with rare elastic lamellae. (1 = elastic media; 2 = elastomuscular media; 3 = muscular media with rare elastic lamellae; 4 = muscular media without elastic lamellae.)

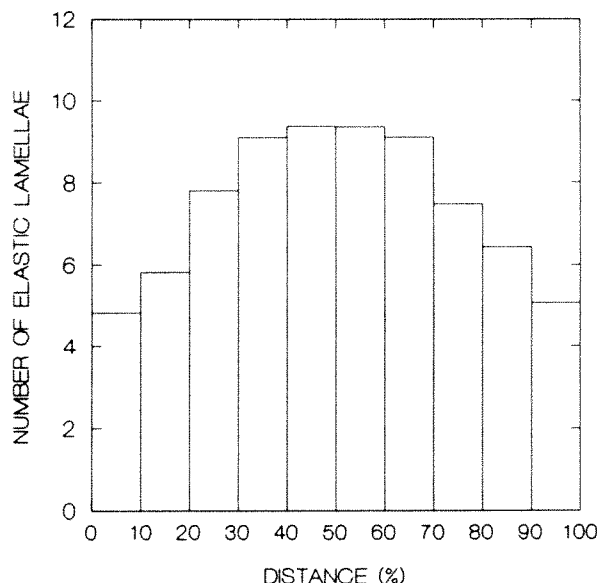


Fig 4. Distribution of the mean number of elastic lamellae in the media of the internal mammary artery along its downstream course.

ential internal elastic lamina of the elastic and elastomuscular segments of the IMA was 18 ± 10 and 35 ± 12 , respectively (mean $\pm$ standard deviation). For the proximal segments of the MPA and the SEA with a muscular media with rare elastic lamellae these numbers were 37 ± 15 and 41 ± 17 , respectively. For the distal segments of the MPA and SEA with a muscular media without elastic lamellae these numbers were 89 ± 31 and 92 ± 39 , respectively. The number of discontinuities in the internal elastic lamina was significantly different among the elastic, elastomuscular, and muscular segments without elastic lamellae (elastic versus elastomuscular, $p = 0.01$; elastic versus muscular without elastic lamellae, $p = 0.001$; elastomuscular versus muscular without elastic lamellae, $p = 0.002$). The number of discontinuities in the internal elastic lamina was not significantly different between the elastomuscular and the muscular segments with rare elastic lamellae. Especially in muscular segments with a great number of discontinuities in the internal elastic lamina we frequently observed single or multiple layers of reduplicated internal elastic lamina, which were present as thin sealing layers on the luminal aspect of the defective internal elastic lamina (Fig 9).

Quantitative Results

The mean cross-sectional luminal area of the proximal elastomuscular and elastic segments of the IMA (both 1.9 mm^2) was significantly greater than that of the distal elastomuscular segment of the IMA (1.2 mm^2) and that of the muscular segments of the MPA (0.9 mm^2) and SEA (0.7 mm^2) ($p < 0.01$). The mean cross-sectional luminal area of the distal elastomuscular segment of the IMA (1.2 mm^2) was significantly greater than that of the distal, purely muscular segments of the MPA (0.9 mm^2) and SEA (0.7 mm^2) ($p < 0.01$), whereas that of the latter two did not differ significantly from that of the proximal segments of

the MPA and SEA with a muscular media with rare elastic lamellae (1.0 mm^2 and 0.8 mm^2 , respectively). Although the cross-sectional luminal area of the IMA along its downstream course gradually decreased, this decrease reached statistical significance only beyond the 90% segment. The small luminal diameter of the IMA, MPA, and SEA in our study is mainly due to rigor mortis and cross-linking contracture of the vessel wall, caused by fixation in 4% formaldehyde solution.

In the 30% to 70% segment of the IMA the number of elastic lamellae (mean, 9) did not vary significantly at the various levels. Obviously, in this primarily elastic segment the number of elastic lamellae was significantly greater than that in the proximal and distal elastomuscular segments of the IMA (mean, 6) ($p < 0.01$) (see Fig 4). The density of the elastic lamellae along the downstream course of the IMA showed a similar pattern (Fig 10).

The absence of elastic lamellae in the media had a profound effect on the degree of intimal hyperplasia: the intima was significantly thicker in the purely muscular

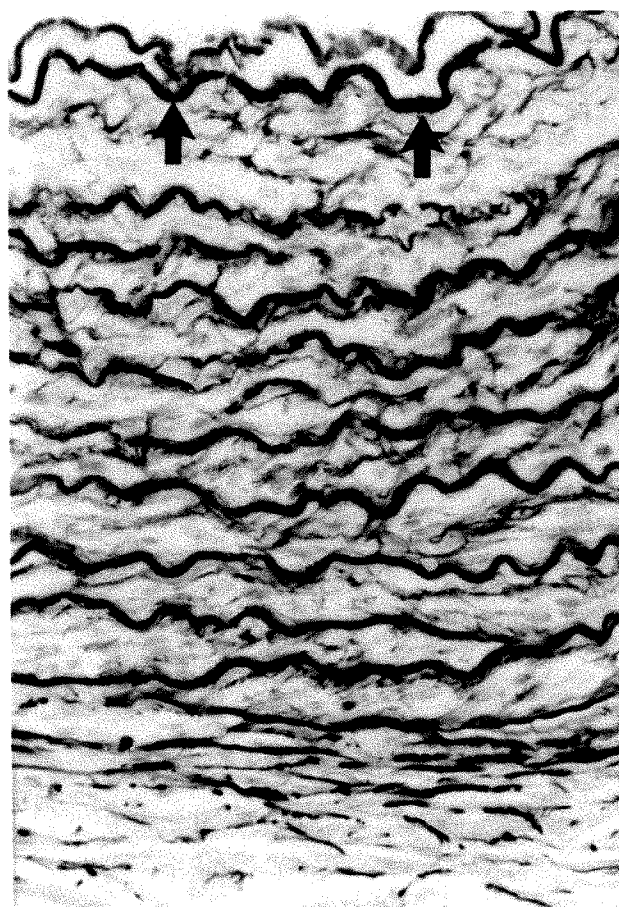


Fig 5. Detail of elastic media at mid level of the internal mammary artery. Note the intact internal elastic lamina (arrows), the absence of intimal thickening, and the moderate presence of smooth muscle cells between the elastic lamellae. The intima consists of a thin layer of endothelial cells, which in this section, due to fixation artifact, is not attached to the internal elastic lamina. (Elastin-trichrome after Masson stain; $\times 400$ before 3% reduction.)

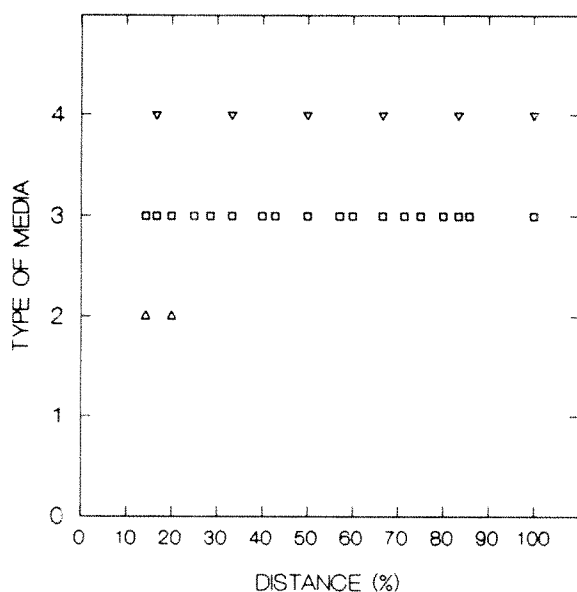


Fig 6. Distribution of the various histological patterns in the media of the musculophrenic artery along its downstream course. Note the predominant presence of a muscular media with or without elastic lamellae. (1 = elastic media; 2 = elastomuscular media; 3 = muscular media with rare elastic lamellae; 4 = muscular media without elastic lamellae.)

segment (25.6%) than in the elastic (16.7%), elastomuscular (15.3%), and muscular (with rare elastic lamellae) (17.5%) segments ($p < 0.01$). The differences in the degree of intimal hyperplasia among the elastic, elastomuscular, and muscular (with rare elastic lamellae) segments were not significant. The degree of intimal hyperplasia also

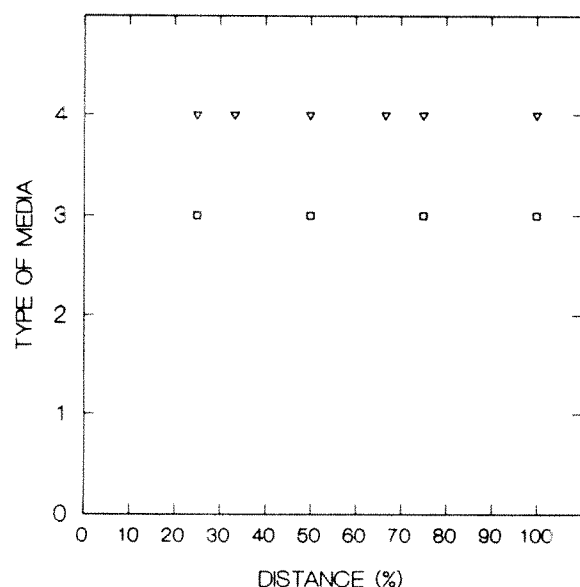
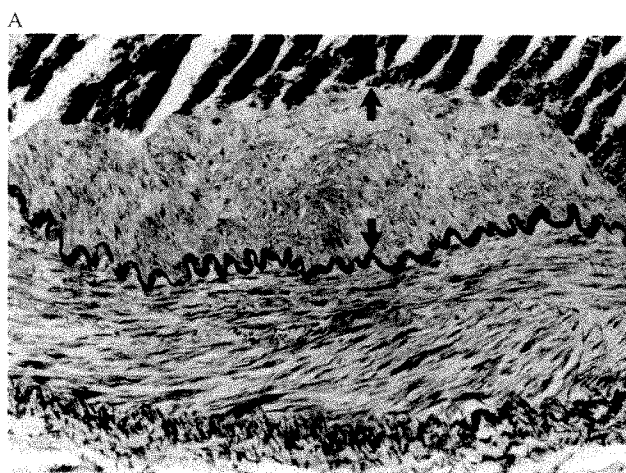
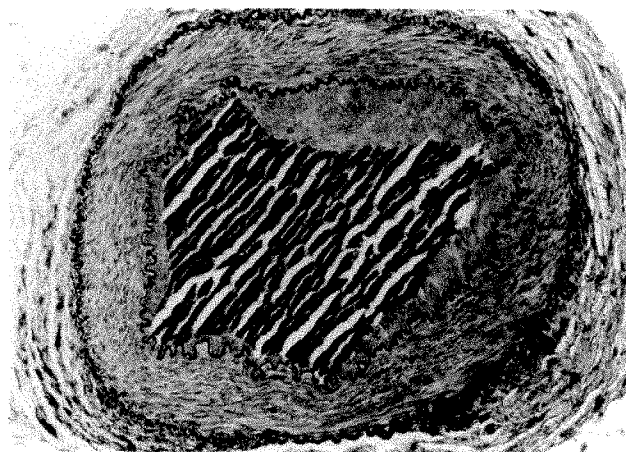


Fig 7. Distribution of the various histological patterns in the media of the superior epigastric artery along its downstream course. Note the presence of a muscular media with or without rare elastic lamellae. (1 = elastic media; 2 = elastomuscular media; 3 = muscular media with rare elastic lamellae; 4 = muscular media without elastic lamellae.)



B

Fig 8. (A) Example of superior epigastric artery 2 cm distal to the epigastric bifurcation, as seen in a considerable number of specimens. Note the circumferential thickening of the intima. (B) Detail. Note the abundant presence of smooth muscle cells in the locally thickened intima (arrows). The media is muscular with rare, incomplete elastic lamellae dispersed in between. (Elastin-trichrome after Masson stain; A: $\times 40$, B: $\times 250$, both before 50% reduction.)

varied along the downstream course of the IMA (being slightly greater in the proximal and distal elastomuscular segments than in the elastic segments), but these differences were not significant.

Comment

In the present study and in another study [5] we observed a correlation between the absence of elastic lamellae in the media and an increased number of discontinuities in the internal elastic lamina, and, as a potential result of this, increased intimal thickening. In the purely muscular segments of the MPA and SEA the intima was significantly thicker than the intima in the more proximal segments of these arteries (muscular with rare elastic lamellae) and the intima in the IMA (elastic or elastomuscular). Although one may argue that these findings may

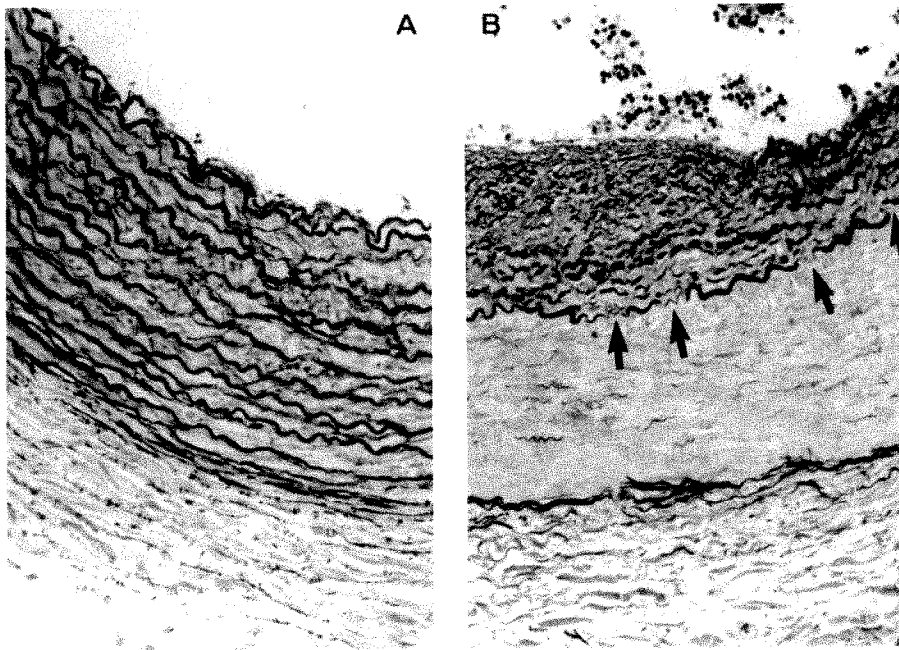


Fig 9. Discrepancy in degree of intimal thickening between mid-segment internal mammary artery (A) and a specimen of a muscular segment of the musculophrenic artery (B), as seen in a considerable number of specimens. (A) Note the multiple elastic lamellae in the media, the relatively intact internal elastic lamina, and the thin intima. (B) In contrast, note the multiple discontinuities in the internal elastic lamina (arrows), the abundant presence of smooth muscle cells in the thickened intima, and the formation of multiple layers of reduplicated internal elastic lamina in the intima. (Elastin-trichrome after Masson stain; $\times 140$ before 30% reduction.)

be coincidentally related but not causally, similar findings are reported in a comparative histological study between the muscular coronary artery and the primarily elastic IMA by Sims and Gavin [6], in which the number of discontinuities in the internal elastic lamina and the degree of intimal thickening were significantly greater in the former vessel. Based on their and our observations we conclude that elastic lamellae in the media may protect against the occurrence of discontinuities in the internal elastic lamina and, secondarily, against intimal thickening,

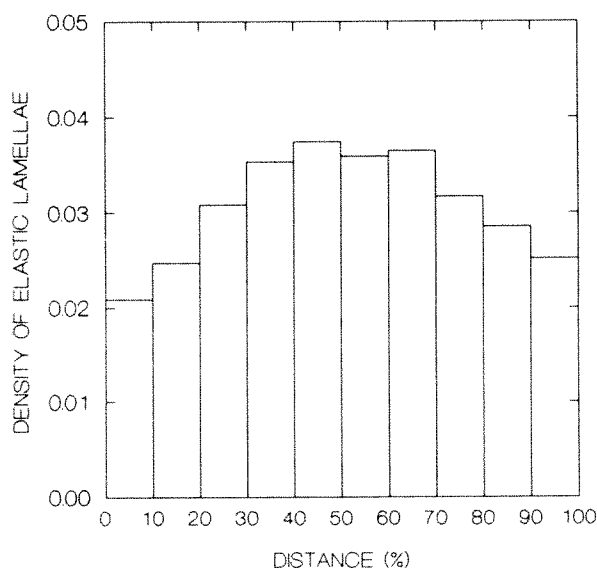


Fig 10. Distribution of the mean density of elastic lamellae (expressed per square micrometer) in the media of the internal mammary artery along its downstream course. Note that the density is highest in the 20% to 70% segment of the internal mammary artery, which is in concordance with the high number of elastic lamellae in this segment (see Fig 4).

ing, even if the number of lamellae is small. The study by Sims and Gavin [6] also suggests that gaps in the internal elastic lamina allow smooth muscle cells of the media to proliferate into the intima and that the rate of this growth reflects the response of medial smooth muscle cells to tension on the arterial wall. Other studies by Sims [7, 8] confirm the structural importance of the internal elastic lamina and its relationship to intimal thickening. Recent research in vascular pathology has shown that medial smooth muscle cells are mesenchymal cells capable of changing from a contractile to a synthetic type in response to damage of the internal elastic lamina and increasing tangential tension on the vessel wall [9]. This process leads to active cell division and synthesis of collagen, elastin, and proteoglycan matrix [10, 11]. The occurrence of discontinuities in the internal elastic lamina enables penetration of proliferating smooth muscle cells from the media into the intima. Within the intima, the proliferating smooth muscle cells produce elastin, often as a coherent reduplicated internal elastic lamina, which can be seen as single or multiple thin sealing layers on the luminal aspect of the defective internal elastic lamina. This phenomenon was frequently observed in our specimens, especially in the MPA and SEA with a purely muscular media. Almost invariably such repair is imperfect, and with the passage of time, breakdown of the reduplicated internal elastic lamina occurs, leading to serious impairment of attachment of endothelial cells, cell loss, and the development of bare areas. Such bare areas may enhance the infiltration of macromolecules of all sizes, including lipoproteins, and cells of the circulating blood, thus accelerating the development of atherosclerotic lesions [12, 13].

Due to the effect of pulsatile stress on the proliferation of smooth muscle cells from the media into the intima the rate of intimal thickening may be enhanced in the central aorta and its branches in comparison with the IMA, in

which the hemodynamics are less vigorous [14, 15]. Such proliferative smooth muscle cell response has been observed in systemic and pulmonary hypertension and in the culture of medial cells from hypertensive animals and from experimental atherosclerosis [16-19]. In our study the degree of intimal thickening was substantially greater in the subclavian artery and the first centimeter of the IMA than in the remainder of the IMA, although this effect was not quantified because it was not the subject of our study. Although no other factor than their intrinsic growth potential would appear necessary to explain the growth of medial smooth muscle cells through defects in the internal elastic lamina to populate the intima, other factors may enhance this rate of growth, and once it has begun, continued increase of intimal thickness throughout life would appear inevitable.

The findings as presented in this study may have implications with regard to selection of the anastomotic site in the IMA. We observed a considerable interindividual variability with regard to the extent of a primarily elastic media in the IMA. In 7 patients the distal segment of the IMA was either elastic or elastomuscular, whereas in 4 patients the distal 10% to 20% segment of the IMA was muscular with rare elastic lamellae. These findings suggest that, based on the assumption that use of an elastic or elastomuscular conduit is superior to use of a primarily muscular one in myocardial revascularization, it may be beneficial not to use the distal 10% to 20% segment of the IMA. This strategy has the additional advantage that the IMA cross-sectional luminal diameter proximal to or at the 80% to 90% level may better match the diameter of the coronary artery than the more distal segment. Selection of the anastomotic site in the MPA or the SEA is not encouraged because of the potentially increased risk of intimal thickening and the significantly smaller luminal diameter of these vessels.

To expand the benefits of the elastic and elastomuscular IMA the shortest possible route to the heart should be established [20-23]. For the same reasons bilateral and sequential grafting with the IMA is beneficial [2-4]. To gain additional length of the IMA transection of the pleura and fascia beneath the IMA may be a valuable technique [24]. However, we do not favor complete or partial skeletonization of the IMA, as advocated by Sauvage and associates [2] and Keeley [25], respectively, because this technique has an increased risk of iatrogenic disruption of the internal elastic lamina, which may be especially deleterious in segments with a high muscular content because it may provoke enhanced intimal thickening [26]. A reported patency rate of free, pedicled IMA grafts approximating that of in situ IMA grafts [27] is consistent with our supposition that the intima and media of the nondiseased IMA are nourished entirely from the lumen [1]. Therefore, any discrepancy in patency rate between in situ and free IMA grafts may be attributable primarily to the proximal anastomosis.

Because of absence of the protective effect of elastic layers in the media on the development of discontinuities in the internal elastic lamina, muscular arterial conduits such as the gastroepiploic artery and the inferior epigas-

tric artery, in analogy to the MPA and SEA, are likely to be more prone to enhanced intimal thickening than elastic and elastomuscular conduits. This hypothesis is supported by one of our previous studies [28] and a study by Suma and Takanashi [29], in which intimal thickening in the right gastroepiploic artery in its natural environment, especially in its proximal segment, was more pronounced than in the IMA. On the other hand, a recent histological study of the inferior epigastric artery in its natural environment suggested a relatively low degree of intimal hyperplasia [30]. Exposure of muscular arterial conduits to the high pressure demands of the ascending aorta, however, may lead to an enhanced rate of intimal thickening, which may prove adaptive to their new environment but also may adversely influence their long-term patency rates. Clinical evidence of accelerated intimal thickening of muscular conduits in myocardial revascularization has been provided by reports of a high occlusion rate of radial artery grafts [31]. Therefore, long-term patency curves of the currently used muscular conduits (mainly the right gastroepiploic and inferior epigastric arteries) must be established before their widespread use in myocardial revascularization can be confidently advised.

Finally, the present study allows some remarks about the vasoregulatory function of the IMA. Although the IMA primarily functions as a pressure reservoir by virtue of the elastic properties of its wall, the elastomuscular and muscular segments of the IMA, MPA, and SEA may have important flow-regulatory functions with regard to perfusion of the anterior chest wall, the mammary gland, the diaphragm, and the rectus abdominis muscle. As such, the muscular and elastomuscular segments of the IMA may be primarily responsible for the wide spectrum of physiologic adaptability of the IMA conduit, vasospasm as observed in low-flow state and enlargement of the IMA in time to meet the high metabolic myocardial demand being the ends of this spectrum [32-34].

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Platelet Protection by Low-Dose Aprotinin in Cardiopulmonary Bypass: Electron Microscopic Study

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To evaluate the effect of low-dose aprotinin during cardiopulmonary bypass on platelet function and clinical hemostasis, 30 patients undergoing various cardiopulmonary bypass procedures employing bubble oxygenators were randomized to receive either low-dose aprotinin (2×10^6 KIU in the cardiopulmonary bypass priming solution, 15 patients [group A]) or placebo (15 patients [group B]). Blood samples were collected before and after cardiopulmonary bypass to assess platelet count and aggregation on extracellular matrix, which was studied by a scanning electron microscope. On a scale of 1 to 4 preoperative mean platelet aggregation grades were similar in both groups (3.8 ± 0.5 and 3.5 ± 0.5 for groups A and B, respectively). Postoperatively, platelet aggregation on extracellular matrix decreased slightly in group A

(2.8 ± 1.3 ; $p < 0.01$) and significantly in group B (1.3 ± 0.5 ; $p < 0.001$). Eleven of the 15 patients in group A remained in aggregation grade 3 or 4 compared with none of the group B patients. Platelet count was similar in both groups preoperatively and postoperatively. Total 24-hour postoperative bleeding and blood requirement were lower in the aprotinin group (487 ± 121 mL and 2.3 ± 1.0 units) than in the placebo group (752 ± 404 mL and 6.8 ± 5.1 units; $p < 0.01$). These results show that the use of low-dose aprotinin during cardiopulmonary bypass provides improved postoperative hemostasis, which might be related to the protection of the platelet aggregating capacity.

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One of the major causes of bleeding after cardiac operations using cardiopulmonary bypass (CPB) is platelet dysfunction [1, 2]. This problem could be overcome by transfusing the patients with fresh whole blood postoperatively [3, 4]. However, in recent years, the use of the protease inhibitor aprotinin during CPB has emerged as a promising prophylactic measure in reducing postoperative bleeding and blood transfusion requirements [5-15]. This clinical effect has been shown [7, 15] to be mediated by preservation of the platelet function.

Most studies reporting the use of aprotinin have used the high-dose regimen, whereby the patient would receive a total of 6 to 7×10^6 KIU aprotinin, starting with a loading dose before sternotomy and continuing during operation. Recently, several studies [7, 16, 17] have reported using the low-dose regimen, whereby only 2×10^6 KIU aprotinin is added to the priming volume of the oxygenator, with good clinical results.

The aim of the present study was to evaluate the clinical effect of using aprotinin in the low-dose regimen employing bubble oxygenators, and to correlate this effect to platelet function. We evaluated platelet function by using the extracellular matrix (ECM) that simulates the in vivo adhesion and aggregation of platelets on the subendothe-

lium [18]. The extracellular matrix is produced by cultured bovine corneal endothelial cells and closely resembles the human vascular subendothelial basal lamina in origin and chemical composition [18]. The ECM has served as an in vitro model in the study of platelet-subendothelial interaction [4, 18-21]. The incubation of human platelets on ECM induces platelet adhesion, aggregation, thromboxane A_2 formation, and a release reaction [18-21]. In the present study, platelet aggregation on ECM was studied with the scanning electron microscope.

Patients and Methods

Thirty patients undergoing various CPB procedures (Table 1) were randomized to receive either low-dose aprotinin (study group [group A], 15 patients) or placebo (control group [group B], 15 patients). The study group received 2×10^6 KIU aprotinin (Trasylol; Bayer, Leverkusen, Germany) added to the priming volume of the oxygenator. No additional aprotinin doses were given to the patients. Each patient in the control group (group B) received equivalent volumes of placebo solution (saline solution 0.9%) added to the priming volume of the oxygenator.

The mean age of the patients was 61 ± 9 years (range, 40 to 78 years), with no difference between the two groups (see Table 1). No patient had been receiving dipyridamole or aspirin-containing drugs during the 4 weeks preceding

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Table 1. Clinical and Operative Data

Variable	Group A: Aprotinin (n = 15)	Group B: Placebo (n = 15)
Age (y)	62 ± 11	60 ± 9
Sex (M/F)	13/2	11/4
Bypass time (min)	145 ± 42	130 ± 48
Aortic cross-clamp time (min)	52 ± 35	40 ± 24
Lowest body temperature (°C)	27 ± 4.8	27 ± 3.7
Procedure		
CABG	9	12
Redo CABG	3	2
Valve replacement	1	1
CABG + valve replacement	2	...

CABG = coronary artery bypass grafting.

the operation. For all patients a Sarns pump (Sarns Inc, Ann Arbor, MI) and bubble oxygenator (Bentley Laboratories, Inc, Irvine, CA) were used. The oxygenators were primed with 1,500 mL of Hartmann's solution and 500 mL of dextrose 5% solution.

The two groups were similar regarding bypass time, aortic cross-clamping time, and lowest body temperature (see Table 1). All patients were rewarmed to 35°C before discontinuation of CPB. Reversal of the heparin effect by protamine was monitored by the activated clotting time.

All pump blood was returned to the patient through the aortic cannula or intravenously by infusion bags without hemoconcentration. None of the patients had to be returned to the operating room because of excessive mediastinal bleeding.

Blood samples from each patient, obtained through a flushed arterial catheter, were collected before and at termination of CPB to assess platelet count and aggregation. Platelet count was measured with a Coulter-Counter-S-Plus II (Luton, England).

Platelet aggregation was evaluated by the ECM model, using a scanning electron microscope [4, 22].

Preparation of Dishes Coated With Extracellular Matrix

Corneal endothelial cells were grown on 24-well-type culture plates (Nunc GmbH, Roskilde, Denmark) with 5% dextran T-40 (Pharmacia, Fine Chemicals, Sweden) added to the growth medium [18, 20, 21]. Cultures were washed once with phosphate-buffered saline (PBS) and exposed to 0.5% Triton-X 100 solution in PBS (volume per volume) followed by exposure to ammonium hydroxide solution, 0.1 mol/L, and washing in PBS. Extracellular matrix-coated dishes containing PBS were stored before use at 4°C for periods up to 3 months.

Platelet Reactivity With Extracellular Matrix

Whole blood, 0.5 mL, in a citrate buffer from each sample was added to the tissue culture well coated with ECM

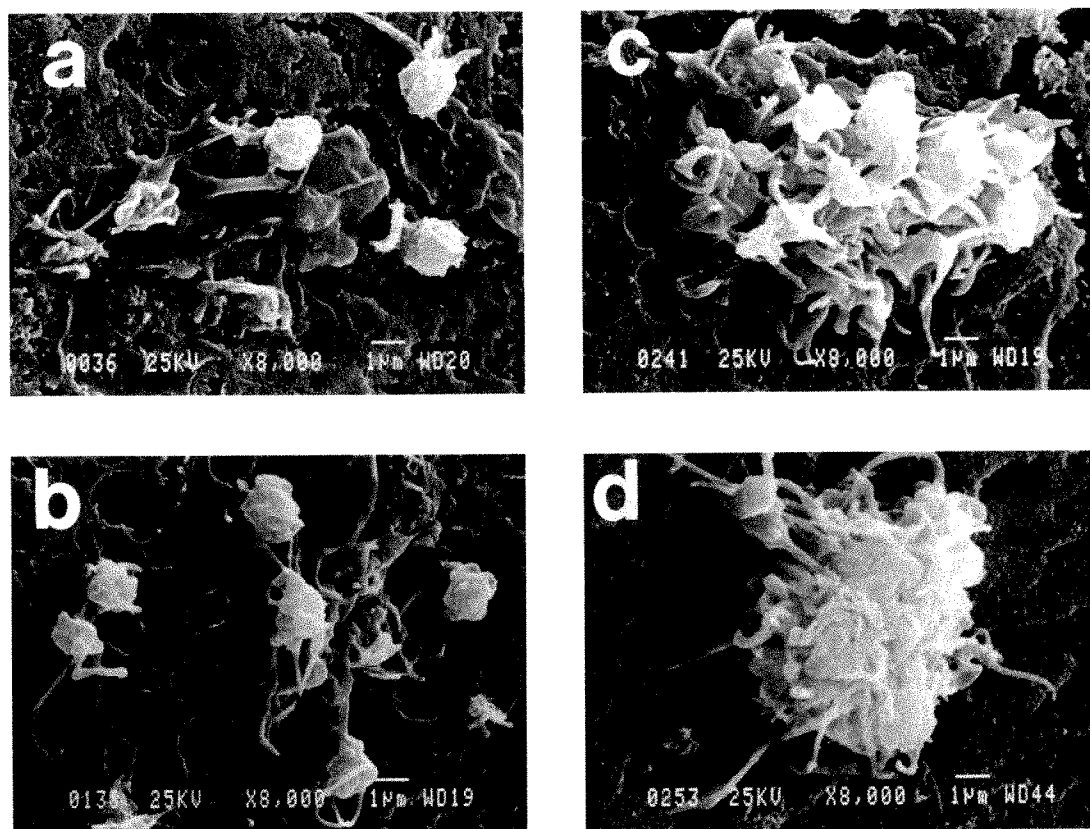


Fig 1. Scanning electron micrographs of the four aggregation grades on extracellular matrix: (a) grade 1; (b) grade 2; (c) grade 3; (d) grade 4. See text for details. (×8,000.)

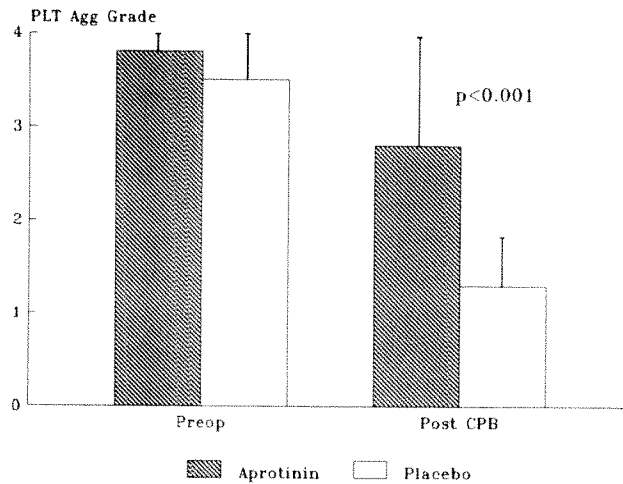


Fig 2. Mean platelet aggregation (PLT Agg) grades of the two groups preoperatively and after cardiopulmonary bypass (CPB).

(16-mm diameter) and shaken (Orbit Shaker, Lab-Line Instruments, Melrose Park, IL; 100 rpm) for 30 minutes at room temperature. At the end of the incubation period, all the blood from the culture dish was collected and the dish was gently flushed several times with PBS.

Preparation for Study With Scanning Electron Microscope

The ECM-coated dishes, now containing platelet aggregates, were fixed by 2.5% phosphate-buffered glutaraldehyde (pH 7.2), then washed in the same buffer and postfixed by osmium tetroxide 2%. The third fixation was by a solution of 2% tannic acid-guanidine hydrochloride. The triple-fixed samples were dehydrated in graded alcohol solutions, and thereafter the alcohol was exchanged to Freon 112 by graded Freon solutions (Du Pont Company, Wilmington, DE). The samples were air-dried, gold-coated, and examined by a Jeol 840 scanning electron microscope (Jeol USA Inc, Peabody, MA).

Grading Platelet Aggregates on Extracellular Matrix

As a method of quantitating the aggregation of platelets on ECM as seen by the scanning electron microscope, four distinct aggregation grades were defined according to the

various platelet morphologic types previously described [23] (Fig 1).

In grade 1 (see Fig 1a), the platelets are discoid with lentiform appearance, have a smooth surface, and lack any pseudopodia. In this grade the platelets do not adhere to each other, and each platelet can be seen individually.

In grade 2 (see Fig 1b), the platelets display the first signs of activation, and they appear with slender dentrite-like pseudopodia, still separated from each other.

In grade 3 (see Fig 1c), the aggregation process is more advanced: The platelet body spreads, showing multiple dentritic pseudopodia, and the platelets start to cluster. In this immature aggregate, each platelet can still be identified separately.

Grade 4 (see Fig 1d) consists of a mature aggregate in which large clumps of platelets are seen and in which individual platelets are difficult to define.

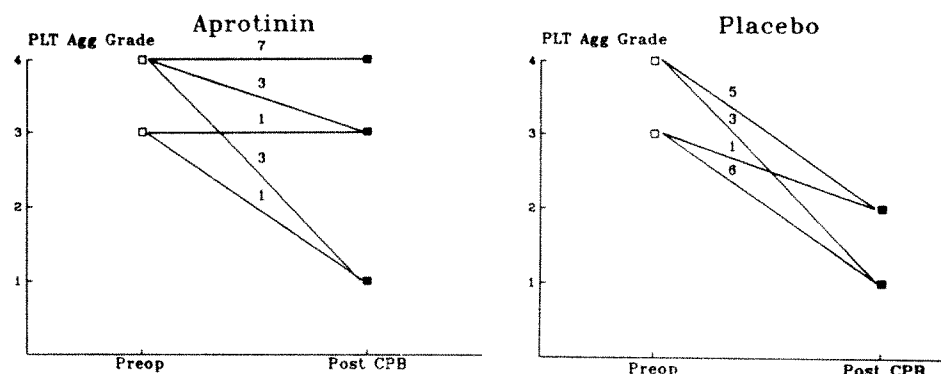
In each sample, 40 scanning electron microscopic fields containing platelets were examined at a magnification of 8,000, each given an individual grade. The final aggregation grade of each sample was derived by calculating the arithmetic mean of the individual grades. Although aggregates of different grades could be found in any given sample, a dominant grade for each sample could always be identified. To avoid any element of subjectivity in the grading process, the observers assigned grades "blindly," that is, they were not aware of the group to which each sample belonged while grading it.

Blood Transfusion Policy

The policy of blood transfusion in the intensive care unit differed in the immediate and late postoperative periods. Most blood transfusions were given in the first 8 postoperative hours. The indications for blood transfusion were hemodynamic parameters, such as low systemic and left atrial pressures, and constricted periphery. The amount transfused depended strongly on the amount of blood lost through the chest tubes. Once the patient's condition had stabilized completely, the indication for further blood transfusion was a hemoglobin level less than 10 g/100 mL. Platelet concentrate transfusions were administered only to patients with active bleeding if platelet count was less than $100 \times 10^9/L$.

Blood loss from the chest tubes, the number of blood

Fig 3. Changes in individual platelet aggregation (PLT Agg) grades in the two groups from before operation to after cardiopulmonary bypass (CPB). Numbers indicate number of patients.



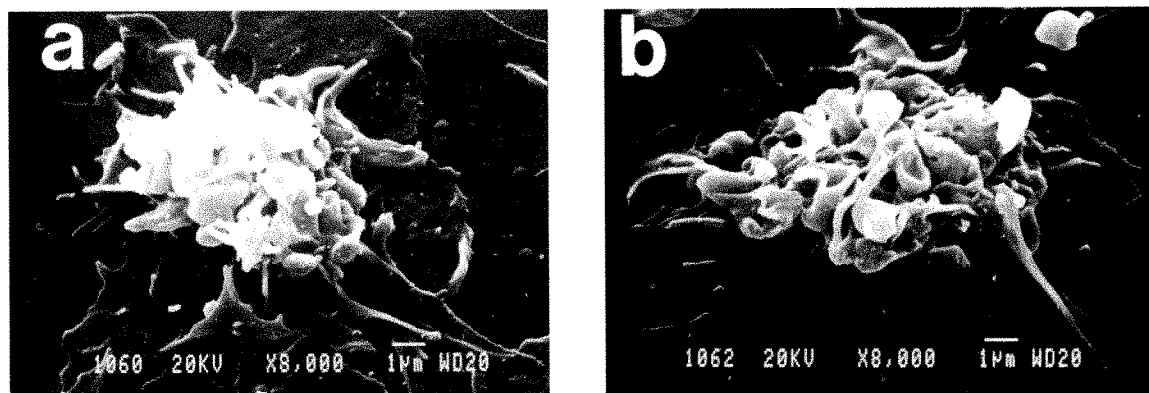


Fig 4. Scanning electron micrographs of a patient from the aprotinin group: (a) preoperative (grade 4); (b) after cardiopulmonary bypass (grade 4). ($\times 8,000$.)

units required, and the total number of blood products transfused (red blood cells, plasma, and platelet units) in the initial 24 hours after the patient arrived at the intensive care unit were recorded for evaluation of clinical hemostasis.

Statistical Analysis

Results were expressed as mean $\pm$ standard deviation. Paired and nonpaired *t* tests were used for parametric variables, and Fisher's exact test and the Mann-Whitney test for nonparametric variables.

Results

Preoperative platelet count in group A (aprotinin group; $172 \pm 44 \times 10^9/L$) did not differ significantly from that in group B ($152 \pm 50 \times 10^9/L$). Similarly, both groups showed significantly lower platelet count after CPB (97 ± 23 and $88 \pm 30 \times 10^9/L$ for groups A and B, respectively; $p < 0.001$), with no significant difference between the two groups.

The mean grade of platelet aggregation on ECM before CPB was similar in both groups (3.8 ± 0.5 and 3.5 ± 0.5 for groups A and B, respectively; $p =$ not significant) (Fig 2). Postoperatively, mean platelet aggregation grade on

ECM was slightly decreased in group A (2.8 ± 1.3 ; $p < 0.01$) and significantly decreased in group B (1.2 ± 0.5 ; $p < 0.001$) (see Fig 2). Eleven of the 15 patients in group A remained in grades 3 or 4, and only 4 could not form aggregates on ECM (grades 1 or 2) (Fig 3). Conversely, all patients in the control group (group B) showed significant decrease of their postoperative aggregation grades to grades 1 or 2, and none showed normal aggregation (see Fig 3). Scanning electron micrographs of patients from each group are shown in Figures 4 and 5.

Total 24-hour blood loss in group A was significantly lower than in group B (Table 2). Patients in the aprotinin group received fewer homologous red blood cell units. Only 1 patient in this group received platelet transfusion, and this accounted for the extremely low exposure to homologous blood products (see Table 2).

Comment

The protease inhibitor aprotinin has been shown in recently published studies to be a promising prophylactic agent in managing CPB-related bleeding [5-14]. We [15] and others [5-14] have shown that when given in a high dose, namely, before and during the entire procedure, aprotinin has the capacity to reduce postoperative blood

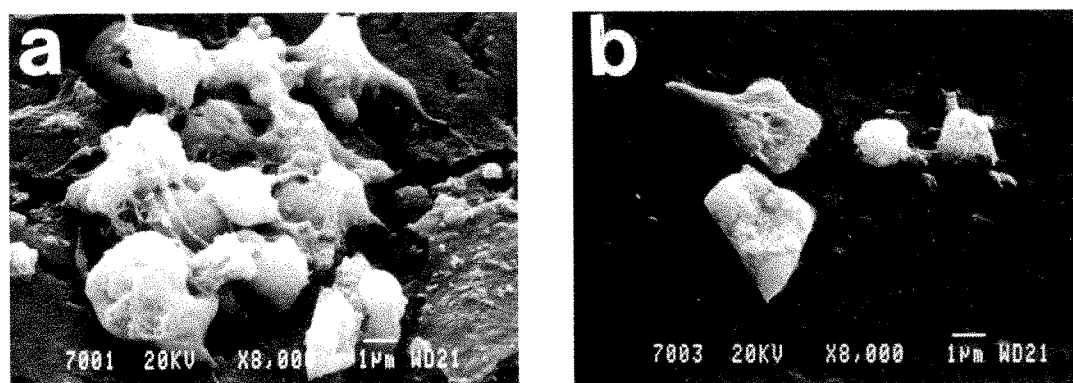


Fig 5. Scanning electron micrographs of a patient from the placebo group: (a) preoperative (grade 4); (b) after cardiopulmonary bypass (grade 1). ($\times 8,000$.)

Table 2. Postoperative Bleeding and Blood Requirement

Variable	Group A (Aprotinin)	Group B (Placebo)	p Value
24-hour bleeding (mL)	487 ± 121	752 ± 404	0.05
RBC (U)	2.1 ± 1.1	3.6 ± 1.8	0.01
Total blood products (U)	2.3 ± 1.0	6.8 ± 5.1	0.01

RBC = red blood cells; Total blood products = RBC + plasma + platelets.

loss and blood transfusion requirement by preserving the platelets' adhesive and aggregatory functions.

As the high-dose regimen was devised on theoretical grounds [14, 24], few attempts have been reported [7, 16, 17] using a low-dose regimen, namely, 2×10^6 KIU aprotinin in the priming solution of the oxygenator. In our study we used the low-dose regimen and demonstrated clinical beneficial results in terms of reduced postoperative bleeding and blood transfusion similar to those observed by previous groups who reported the use of the low-dose regimen [7, 16, 17].

Moreover, using the ECM model we have shown that the improved clinical hemostasis observed with the low-dose aprotinin regimen may be attributed to the partially preserved platelet aggregatory capacity. Seven of the 15 patients who received low-dose aprotinin maintained normal platelet aggregation (grade 4) after CPB, and another 4 displayed near-normal aggregation (grade 3), as opposed to none of the placebo group patients, who all displayed deranged aggregation (grades 1 and 2). Similar results, albeit somewhat better, were shown by us when the high-dose aprotinin regimen was tested [15]. In that group all patients maintained normal or near-normal platelet aggregation after CPB.

Previous reports [7, 25] have correlated the improved hemostasis provided by aprotinin to the preservation of the platelet glycoprotein Ib-dependent adhesive capacity. By using the ECM model as an in vitro model for the study of platelet subendothelium interaction [18-21], we have demonstrated an additional effect of CPB on platelets represented by the deranged aggregatory capacity found in all patients in the placebo group, who showed some platelet adhesion to the ECM (grades 1 and 2), but no signs of aggregation. The lack of aggregation on ECM in the placebo group might be due to fibrinogen receptor defect, as Glanzman's thrombasthenic platelets (which are deficient of glycoprotein IIb/IIIa) exhibit the same response to ECM [19]. These results concur with those of Rinder and colleagues [26, 27], who have shown selective decreases in platelet glycoprotein IIb/IIIa, in addition to Ib, as a result of CPB. The assumption that other agonists present in the ECM, such as collagen or fibronectin, might be responsible for the improved aggregation found in those patients who received aprotinin is negated by the fact that those agonists did not play any role in the placebo group.

It should be noted that the discrepancy in the mode of action of aprotinin between our observation and that of others [7, 25] may be explained at least partially by the use

of bubble oxygenators in our study and membrane oxygenators by the others. It is known that platelet aggregation is better preserved by membrane than by bubble oxygenators [28].

As platelet aggregation on ECM requires both fibrinogen [19] and von Willebrand's factor [29] as ligands for the activated glycoprotein IIb/IIIa, our model is not sensitive enough to differentiate which domain on the glycoprotein IIb/IIIa was protected by aprotinin. The preserved aggregatory capacity of platelets in the aprotinin group of our study suggests that at least part, if not all, of the glycoprotein IIb/IIIa was protected.

A possible explanation for the protective effect of aprotinin on blood loss during CPB has recently been suggested [14, 30]. According to this hypothesis, plasmin, generated during CPB, activates the platelets and causes changes in the distribution of glycoproteins IIb/IIIa and Ib on the platelet's membrane [31]. This effect is further enhanced by the lower temperatures used for the CPB procedure [32]. Activated platelets might become nonreactive or cleared from the blood by interaction with components of the CPB system, and thus bleeding tendency is increased. Aprotinin, by its known antifibrinolytic effect [33, 34], may protect postoperative platelet aggregation by inhibiting the high deleterious plasmin level [33]. Our study has not addressed the antifibrinolytic effects of aprotinin but has shown that the final pathway, namely, platelet aggregatory capacity, is preserved by the drug.

We conclude that the use of low-dose aprotinin during CPB, using bubble oxygenators, provides improved postoperative hemostasis by preserving the platelet aggregatory capacity. These beneficial effects of aprotinin have reconfirmed the utmost importance of platelets in postoperative hemostasis.

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Bovine Internal Mammary Artery as a Conduit for Coronary Revascularization: Long-Term Results

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Graft patency after coronary artery bypass grafting depends largely on the choice of conduit. Because an increasing number of patients have insufficient or poor-quality autologous material, there is a need for a suitable synthetic graft that is readily available and easy to handle and that has good long-term patency. Early results suggest that the bovine internal mammary artery graft may meet these criteria. We have used a total of 26 such grafts in 18 patients. Postoperative angiography has been performed in 19 grafts in 14 patients, 3 to 23 months after operation; of these grafts, 3 are currently patent

(15.8%, compared with 85.7% and 75.0% patency for native internal mammary artery and saphenous vein grafts in the same patients). We report the results of clotting studies and an analysis of lipid status. These patients do not, however, appear to represent any atypical group, either in terms of coagulopathy, native coronary artery size, or the type of vessel disease. Nevertheless, our poor results contrast markedly with the early enthusiasm reported from other centers.

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During the last decade many countries have witnessed a dramatic increase in the number of patients undergoing coronary artery bypass grafting. As a consequence, the number with insufficient or inadequate autologous vessels suitable for use as coronary artery grafts is also increasing. These patients may include those who have had previous heart operations and those with bilateral varicose veins, either with or without a previous history of surgical intervention such as sclerotherapy or vein stripping.

A successful outcome after coronary artery bypass grafting does, however, depend very much on the choice of graft conduit. Saphenous vein is still the most commonly used material with 45% to 50% of conduits remaining patent at 7 years [1, 2]. More recently, however, the internal mammary artery has been used and has been shown to have even better long-term patency with approximately 94% of grafts still functioning over the same time span [1-3]. Bilateral internal mammary artery grafts [4] and right gastroepiploic artery grafts [5] are similarly successful.

Many other natural and synthetic graft materials have been used, but unlike the conduits described above, none have achieved comparable success. These materials include arm veins (20% patency at 5 years) [6], umbilical veins, and polytetrafluoroethylene grafts [7, 8].

Recently, bovine internal mammary arteries have become commercially available (Bioflow; Bio-Vascular Inc, Saint Paul, MN). Initial experience using these for coronary artery bypass suggests early patency rates of 85% at

6 months [9]. This study addresses the question of long-term patency.

Material and Methods

In the 2-year period between January 1990 and December 1991, 26 bovine internal mammary artery grafts (Bioflow; Somatech, Oxford, UK) were implanted into 18 patients. In each case, previous operation or saphenous varicosity limited the availability of autologous graft material and consent was therefore obtained for heterologous conduits to be used. There were 13 men and 5 women, with a mean age of 61 years (range, 52 to 71 years). Two patients had had previous coronary artery operations, and 1 of these and 3 others underwent concurrent mitral or aortic valve replacement or repair. Two were insulin-dependent diabetics.

In each case cardiopulmonary bypass and suture techniques followed a standard pattern, distal anastomoses being carried out with continuous 6-0 Prolene (Ethicon, Edinburgh, UK) and proximal anastomoses with continuous 5-0 Prolene; 4 mm conduits were used in 2 patients and 3 mm in the remainder. Endarterectomy was required in 6. Details of the vessels grafted with bovine internal mammary arteries are listed in Table 1. In this group of patients, however, a total of 21 other vessels were also grafted, using native internal mammary arteries in 10, autologous saphenous vein in 10, and the inferior epigastric artery in 1. Where the native left internal mammary artery was available, it was used to graft the left anterior descending artery. When saphenous vein was the only native conduit available, it was used to graft the most important vessel based on the particular angiographic findings.

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Table 1. Bovine Internal Mammary Artery Graft Positions in 18 Patients

Vessel	No. of Grafts	Vessel size (mm)		No. With Distal Disease
		Range	Mean	
LAD	8	1.0-2.5	1.75	2
Circ	5	2.0-3.0	2.25	0
RCA	13	1.0-3.5	2.00	5

Circ = circumflex artery or its branches; LAD = left anterior descending artery; RCA = right coronary artery or posterior descending artery.

After operation, four anticoagulant policies were used. Three patients received only aspirin (75 mg daily), 8 received only warfarin, 4 received both aspirin and warfarin, and 3 received warfarin and dipyridamole.

Two patients died, 1 at 10 months because of cardiac failure and the other at 4 months, following myocardial infarction. Two patients have been readmitted to a hospital with severe angina on more than one occasion; each has recently had a large myocardial infarction and both refused restudy. With informed consent, however, the remaining 14 patients were admitted for reinvestigation at a mean of 9.5 months after operation (range, 3 to 23 months). After clinical assessment, each patient underwent angiography; 6F catheters were inserted by a femoral approach and each native vessel and graft (prosthetic and autologous) was selectively restudied. Digital subtraction angiography was also performed whenever selective exploration of the ascending aorta had failed to reveal all the expected grafts. In addition to angiography, blood was collected for measurement of the following parameters: urea and electrolyte concentrations, liver function tests, low-density and high-density lipoprotein cholesterol concentrations, lipid profiles, plasma viscosity, fibrinogen concentrations, platelet function tests, and a clotting screen.

Results

In 18 patients receiving bovine internal mammary artery grafts, 13 complained of recurrent angina. This was mild in 5, but myocardial infarction occurred in 4.

Of the 19 bovine internal mammary grafts restudied, only 3 were patent (15.8%). The results are summarized in Table 2 and compare with patency rates of 85.7% for native internal mammary arteries and 75.0% for saphenous veins.

Three patients had acute episodes of chest pain requiring hospital admission shortly before they were restudied;

Table 2. Patency Rates in 14 Patients Restudied 3 to 23 Months After Operation

Graft Type	No. of Grafts	No. Patent	Patency Rate
Bovine IMA	19	3	15.8%
Native IMA	7	6	85.7%
Vein	8	6	75.0%
Epigastric artery	1	0	0%

IMA = internal mammary artery.

in 1, myocardial infarction had occurred. The grafts were blocked in all 3 patients, raising the possibility of occlusion being an acute event. Severe chest pain developed in 1 further patient on the tenth postoperative day; emergency angiography revealed a patent bovine internal mammary graft, but early intraluminal irregularity. Restudy at 6 months showed total occlusion.

There were no abnormalities in the lipid or cholesterol profiles, electrolytes, liver function tests, or fibrinogen concentrations. Each patient taking warfarin was found to be adequately anticoagulated; only 4 of 7 patients taking aspirin, however, had reduced platelet aggregation in response to arachidonic acid stimulation. Anticoagulant policy did not appear to affect the patency rate of bovine internal mammary grafts in this series.

Comment

The ideal artificial graft for coronary artery bypass should be of small diameter, freely available (and in different sizes), inert, pliable and easy to use, and associated with good long-term patency. Bioflow bovine internal mammary artery grafts are harvested from cows, treated with dialdehyde, and sterilized with ethanol and propylene oxide. They are therefore inert and freely available, so meeting two of the criteria for an ideal artificial conduit.

Early laboratory work in dogs suggested that bovine internal mammary artery grafts had a lower thrombogenicity than polytetrafluoroethylene grafts at 3 months [10] and were suitable for coronary artery bypass. Clinical use was first reported in 1988 [11], and although subsequent studies support the use of these grafts, only one has actually restudied graft patency [9]. In this, 11 of 13 bovine internal mammary artery grafts (85%) were patent at 6 months, but there is no mention of anticoagulant policy. Our report of "long-term" bovine internal mammary artery graft patency is in complete contrast to these results from elsewhere, as we have found only 15.8% patency in 19 grafts restudied 3 to 23 months after implantation.

Reinvestigation of native internal mammary artery and saphenous vein graft patency in the same patients, is by comparison, consistent with results from other centers [1, 2]. Because the same suture techniques were used for all types of graft, because these compare with techniques reported elsewhere [12], and because more than one surgeon implanted our grafts, it is unlikely that surgical method is to blame for the poor results we have found. Similarly, the type of coronary artery disease and the nature of the vessels grafted appear to be a typical cross-section of our practice, and there is no indication that bovine grafts were only used in unfavorable circumstances. In addition, platelet studies and clotting studies also demonstrate that this group of patients represented a normal sample of the postoperative population and were not atypically hypercoagulable.

Three patients nominally taking aspirin were, however, found to have normal rather than reduced platelet function, suggesting either that they were noncompliant with their medication or that a standard dose of 75 mg once per

day may be inadequate in certain individuals. Nevertheless, the nature of the postoperative anticoagulant policy did not appear to influence graft patency, and we therefore conclude that the observed poor performance of the bovine internal mammary artery grafts is due to genuine graft failure and unlikely to be due to technique or abnormal coagulation.

The dialdehyde tanning procedure removes the dendritic cells of the bovine internal mammary artery grafts, so rendering them immunologically inert. Rejection is therefore unlikely to be a cause of their failure. However, with exposure of collagen and the inevitable lack of endothelium in the intima, the nonliving tissue of the conduit (despite favorable laboratory studies) must represent a very thrombogenic surface. With this knowledge, poor long-term patency is not surprising, and in view of our results, we cannot recommend further use of this graft. Although bilateral (native) internal mammary artery grafts could be performed, we did not use this approach. This was partly because the right internal mammary artery was often found to be unsuitable in view of the location of the vessels to be grafted and also because of concern over the consequences of sternal devascularization. Although other arterial conduits such as the gastroepiploic artery may be helpful in some instances, there is clearly a need for a satisfactory artificial graft. Nevertheless, we believe that the ideal conduit still remains to be found.

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Perfusion Pressure Control by Adenosine Triphosphate Given During Cardiopulmonary Bypass

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Administration of exogenous adenosine triphosphate (ATP) as a vasodilator during cardiopulmonary bypass was assessed in consecutive adult patients ($n = 24$) who demonstrated a high arterial perfusion pressure (mean, >90 mm Hg). The action of ATP was characterized by rapid induction and stabilization of the blood pressure level. The dose of ATP ranged from 0.68 to 2.68 mg/min. Within 1 minute after the administration, there was a significant reduction in the perfusion pressure from 102 ± 18 mm Hg (mean $\pm$ standard deviation) to 72 ± 19 mm Hg. The ATP was then able to maintain the desired pressure of 69 ± 12 mm Hg at 5 minutes, 67 ± 12 mm Hg at 10 minutes, and consistent values thereafter. After the ATP administration was discontinued, there was a prompt recovery of pressure without bradyar-

rhythmia. The frequency and amount of inotropes used were consistent with the control group ($n = 26$). Although the administration of ATP reduced the increase in serum catecholamine concentration, there were no significant changes in other vasoactive mediators (eicosanoid, angiotensin II, endothelin) between the two groups during cardiopulmonary bypass. There was neither an accumulation of metabolic products (uric acid, phosphate) nor a decrease in the level of divalent cation (Ca^{2+}), which is observed when the cations combine with phosphates or adenosine nucleotides. This study confirmed the efficacy and safety of ATP infusion during cardiopulmonary bypass.

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Peripheral vasculature usually constricts during cardiopulmonary bypass (CPB), especially during central cooling. This response is generally believed to be due to the increase in the level of catecholamine [1-4]. To improve the impaired peripheral vascular circulation, several kinds of vasodilators have been used. Although chlorpromazine is an effective vasodilator [5], the negative and uncontrollable inotropic effect is often problematic. α -Adrenergic blocking agents, such as phentolamine or phenoxybenzamine, have delayed initiation periods and prolonged durations of action. Nitroglycerin also has a delayed effect and is unpredictable. The use of prostacyclin has been reported to be beneficial for not only vasodilatation, but also platelet protection, in spite of its high cost [6, 7]. Because rapidly acting vasodilators are clinically important for the acute control of blood pressure, sodium nitroprusside has been used in the United States and other countries [8, 9]. However, the clinical use of sodium nitroprusside has been prohibited in various countries, including Japan, because of the possible toxicity of its metabolite (cyanide) [10-12]. Thus, alternative and cost-effective vasodilators are required.

Adenosine triphosphate (ATP) is a well-known intracellular high-energy molecule. Studies on the cardiovascular

effects of exogenously administered ATP have shown that ATP is a potent vasodilator [13-16] with negative inotropic [17] and chronotropic properties [18]. The concentration of ATP that is required to obtain the negative inotropic and chronotropic effects is rather high compared with the concentration needed to induce vasodilation. Therefore, a small dose of ATP is able to induce vasodilation without manifesting the other effects. In addition, ATP administration may also influence vasoactive mediators, which could additionally affect the vasoactive mechanisms.

This study was designed to evaluate the vasodilative effects of ATP, to then examine its influence on vasoactive mediators, and finally to determine its safe and efficient administration during CPB.

Material and Methods

Fifty consecutive adult patients who underwent open heart operations were included in this study. Four hundred milligrams of ATP (10 mL) was prepared in 90 mL of saline solution. When the mean arterial perfusion pressure exceeded 90 mm Hg, ATP was administered to maintain the mean pressure around 65 mm Hg. Consequently, ATP was used in 24 of the 50 patients.

Anesthesia and Cardiopulmonary Bypass

The patients were premedicated with morphine (0.08 mg/kg) and scopolamine (0.06 mg/kg) 1 hour before

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the induction of anesthesia. Before the induction, a Swan-Ganz catheter was inserted through their right internal jugular vein. Balanced anesthesia was introduced with fentanyl ($10 \mu\text{g/kg}$), diazepam, and pancuronium bromide. A membrane oxygenator, with polypropylene hollow fibers and polyvinyl chloride tubing, was used for the operation. Before the initiation of the bypass, 2 g of hydrocortisone and heparin (2 mg/kg) were administered intravenously. The operation was performed in moderate hypothermia (around 28°C) with partial hemodilution (estimated hematocrit, 0.25), and the activated clotting time was maintained at more than 400 seconds with intravenous additions of heparin. Cardiac arrest was obtained with a potassium cardioplegic solution. The heart was then topically cooled. Finally, we tried to maintain the perfusion flow at $80 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ while performing the total bypass.

Measurements of Vasoactive Mediators

In 15 patients (8 with ATP administration and 7 controls), the levels of the vasoactive mediator metabolites of eicosanoid (thromboxane B_2 and prostaglandin $F_{1\alpha}$), endothelium-derived constrictive factor (endothelin 1), catecholamine (norepinephrine and epinephrine), and angiotensin II were measured. Measurements were carried out after the anesthesia, 5 minutes after the initiation of CPB, and 5 minutes before the cessation of CPB. Inotropes were not used during this period. The methods used to measure these substances are described elsewhere [4, 19].

Adenosine Triphosphate Metabolism

After intravenous administration, the capillary endothelial cells rapidly hydrolyze ATP to adenosine with the consequent release of three molecules of phosphoric acid. Although adenosine is rapidly deaminated and converted to hypoxanthine, which is subsequently oxidized to uric acid [20], adenosine nucleotides and phosphates may form complex divalent cations such as calcium. In all of the patients, serum concentrations of ionized calcium, phosphate, and uric acid were measured at the beginning and end of CPB.

Statistical Methods

All values were expressed as the mean $\pm$ standard deviation. The unpaired Student's *t* test was used to determine the statistical significance of differences between the two groups. Differences with a *p* value of 0.05 or less were considered significant. The coefficient of correlation between two variables was calculated using Spearman's rank-difference technique.

Results

There were no differences in either the operative procedures or the ages between the experimental and control groups (Table 1). The body temperatures and perfusion flows during CPB were also identical. The average aortic clamping time was 76 ± 39 minutes in the control group and 90 ± 40 minutes in the ATP group (*p* = 0.23). The

Table 1. Operative Procedures

Variable	ATP Group	Control Group
No. of patients	24	26
Age (y)	54 ± 7	54 ± 11
Disease		
Congenital	1	2
Acquired		
CABG	8	11
Valve	15	10
Others	0	3

ATP = adenosine triphosphate; CABG = coronary artery bypass grafting.

average perfusion time was also shorter (*p* = 0.11) in the control group (125 ± 59 minutes) than in the ATP group (154 ± 59 minutes). The initial arterial pressure was 52 ± 11 mm Hg in the control group and 55 ± 16 mm Hg in the ATP group, with peak pressures of 73 ± 9 mm Hg and 102 ± 18 mm Hg, respectively (*p* < 0.01).

In the ATP group, the dose of ATP ranged from 0.68 to 2.68 mg/min with a mean dose of 1.28 ± 0.56 mg/min. The total mean dose of ATP was 78 ± 57 mg (from 6.6 to 240 mg) with a mean infusion period of 55 ± 25 minutes. Figure 1 displays the changes in mean arterial pressures that were regulated by the administration of ATP during CPB. A significant drop in arterial pressure was observed within 1 minute (usually 20 to 30 seconds) after the initiation of ATP administration. The perfusion pressure was then maintained at the desired pressure of 68 ± 16 mm Hg (at 3 minutes) and remained consistent thereafter. After the discontinuation of ATP administration, a prompt recovery in arterial pressure was observed. Because the patients did not display episodes of either second-degree or complete atrioventricular blockage or bradycardia after CPB, they did not require any additional treatments. The frequency of inotrope use was not signif-

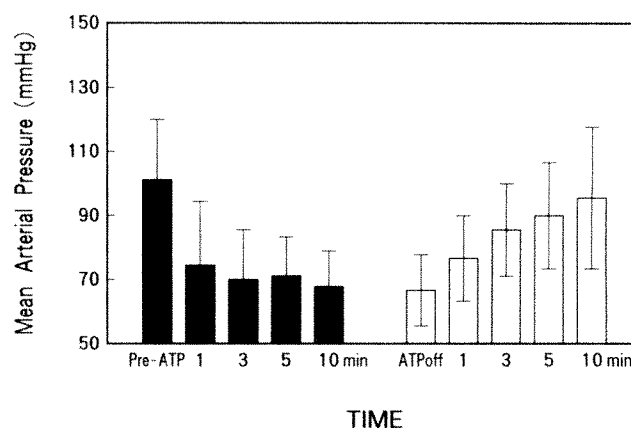


Fig 1. Transit of arterial perfusion pressure maintained by adenosine triphosphate (ATP) administration. Administration of ATP was characterized by rapid induction and stabilization of the blood pressure level; after discontinuation, a prompt recovery in pressure was observed.

Table 2. Changes in Vasoactive Mediators

Vasoactive Mediator	Anesthesia	CPB On	CPB Off	Change
Thromboxane B ₂				
ATP	28 ± 13	243 ± 243	364 ± 252	121 ± 151
Control	28 ± 7	247 ± 185	379 ± 132	133 ± 152
Prostaglandin F _{1α}				
ATP	47 ± 18	248 ± 152	211 ± 139	-36 ± 72
Control	61 ± 19	252 ± 113	244 ± 146	-8 ± 222
Angiotensin II				
ATP	98 ± 33	114 ± 100	96 ± 69	-18 ± 45
Control	91 ± 65	75 ± 28	131 ± 92	56 ± 89*
Norepinephrine				
ATP	123 ± 74	294 ± 168	353 ± 168	60 ± 107
Control	122 ± 90	267 ± 44	481 ± 111	214 ± 87*
Epinephrine				
ATP	31 ± 16	195 ± 116	161 ± 129	-34 ± 97
Control	38 ± 23	149 ± 54	395 ± 198	246 ± 165
Endothelin				
ATP	1.5 ± 0.8	2.1 ± 0.7	2.3 ± 0.4	0.2 ± 0.4
Control	1.6 ± 0.7	2.7 ± 1.0	3.2 ± 0.8	0.6 ± 0.7

* $p < 0.01$, ATP versus control.

ATP = adenosine triphosphate; Change = value change from CPB on to CPB off; CPB = cardiopulmonary bypass.

icantly different between the two groups (ATP, 18 of 24 patients; control, 20 of 26).

The increase in the concentrations of serum thromboxane B₂ and prostaglandin F_{1α} concentrations during CPB was not influenced by the administration of ATP. In addition, the concentrations of angiotensin II and endothelin also did not display significantly varying results. The increments of norepinephrine and epinephrine, however, were significantly less in the ATP group during CPB (Table 2).

The measured serum concentrations of calcium, phosphate, and uric acid were not different between the two groups both preoperatively and postoperatively (Table 3). There was little correlation between the total ATP dose and the increase in the level of uric acid (preoperative minus postoperative value) during CPB ($r = -0.15$; $p = 0.51$).

Comment

Adenosine triphosphate-induced vasodilatation is characterized by rapid induction and stabilization of the blood

Table 3. Levels of Uric Acid, Calcium, and Phosphate

Variable	ATP Group		Control Group	
	CPB On	CPB Off	CPB On	CPB Off
Uric acid	5.3 ± 1.3	5.4 ± 1.0	5.4 ± 1.9	5.6 ± 2.0
Calcium	3.0 ± 0.3	3.4 ± 0.3	3.0 ± 0.3	3.7 ± 1.7
Phosphate	2.5 ± 0.6	2.3 ± 0.7	2.5 ± 0.9	2.3 ± 1.0

* No statistically significant differences were observed between ATP and control groups.

ATP = adenosine triphosphate; CPB = cardiopulmonary bypass.

pressure level, which rapidly reverses when infusion of the drug is discontinued. This abrupt response is due to the rapid metabolism of ATP [20]. The mechanisms of ATP vasodilatation are mainly endothelium-dependent relaxation caused by endothelium-derived relaxing factor release [13, 14, 16, 21]. Endothelium-derived relaxing factor has been previously described as a vasodilator messenger between the endothelial cell receptors (endothelial-dependent relaxing agents such as acetylcholine, histamine, peptides, adenosine diphosphate, and ATP) and the effector (vascular smooth muscle cells). Endothelium-derived relaxing factor consequently increases the level of cyclic guanosine monophosphate in the smooth muscle and dilates the vessels [16, 21]. In addition to these actions, ATP produces peripheral vasodilatation by inhibiting of the sympathetic nervous system [13]. Perhaps the effectiveness of ATP as a vasodilator is influenced by some modulation (hypertension or atherosclerosis) of the endothelium and sympathetic nerve intensity during CPB. However, because all our patients did not show a blunt reaction to ATP administration, the effectiveness of ATP's vasodilative action was not altered by individual modulation of the endothelium or by general anesthesia during CPB.

Sodium nitroprusside is also a short-acting antihypertensive agent with an effect that ceases immediately after the infusion is stopped. However, when administered in high doses, it is potentially toxic because the normal metabolic pathways can become overloaded. In addition, free cyanide is formed, which is capable of destroying cytochromes [10-12]. Moore and associates [12] examined the effect of hypothermia on the metabolism of sodium nitroprusside during CPB. They concluded that the non-enzymatic release of free cyanide from sodium nitroprusside was not inhibited by hypothermia, whereas the enzymatic detoxification of free cyanide was possibly delayed. As Fukunaga and colleagues [15] demonstrated, ATP has a more rapid initiation period and shorter recovery time than sodium nitroprusside. Moreover, the administration of ATP maintained a remarkably stable blood pressure throughout the infusion [15].

For the treatment of reentrant tachycardia, the dose of ATP bolus injection has been reported to be between 15 to 30 mg [18]. However, the continuous low-dose infusion (0.68 to 2.68 mg/min) of ATP during CPB in this study did not induce bradycardia after aortic declamping. In addition, because negative inotropic and chronotropic effects were not reported during ATP-induced hypotensive anesthesia, the influence of ATP on postischemic cardiac functions was considered negligible [22-24]. Most hemodynamic changes induced by ATP infusions are related to changes in vascular resistance rather than changes in myocardial contractility [22-24].

Other investigators have demonstrated that ATP administration not only inhibits norepinephrine release in blood vessels and other organs [25] but also inhibits the action of epinephrine on vascular smooth muscles in experimental animals [23]. It was also reported that ATP administration during operation on a pheochromocytoma depressed the induction of both hypertension and ar-

rhythmia induced by catecholamine release [26]. During CPB, because the increase in the level of catecholamine induces an increase in vascular resistance [1-4], the administration of ATP is very effective and theoretically recommended. Although low levels of catecholamine were detected in this study, these low concentrations might be involved in protecting against reperfusion injury [27, 28]. The administration of ATP did not influence the other vasoactive mediators.

There was neither an increase in serum uric acid nor a decrease in the level of serum calcium in the ATP group after CPB. These were the same results observed in the control group. Furthermore, we did not detect any complications due to the process of ATP metabolism or the metabolites. Therefore, the side effects of ATP administration were negligible.

In conclusion, the administration of ATP during CPB is a very effective procedure to control high blood pressure. Because the application of ATP is both effective and safe, this drug can be used as a substitute for sodium nitroprusside.

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Effects of Cryothermia During Cold Cardioplegia on Epicardial and Intramural Coronary Arteries

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Cryosurgery is playing an increasingly important role in the surgical treatment of various supraventricular and ventricular tachyarrhythmias. The short-term and long-term effects of cryogenic injury on epicardial and intramural coronary arteries were studied in 22 dogs. Transmural cryolesions encompassing a posterolateral branch of the circumflex coronary artery were produced in the inferior left ventricular wall during extracorporeal circulation and cold cardioplegic arrest. The mean epicardial cryolesion area $\pm$ standard deviation was $10.4 \pm 1.8 \text{ cm}^2$. The mean epicardial coronary artery diameter $\pm$ standard deviation measured $1.2 \pm 0.4 \text{ mm}$. At 6 hours, no

important structural changes were noted in any of 6 dogs. At 48 hours, 1 of 2 epicardial coronary arteries showed recent thrombus. At 1, 3, and 6 months, the epicardial coronary arteries were occluded due to thrombosis and intimal hyperplasia in 13 of 14 dogs. A limited degree of recanalization was observed. At all follow-up intervals, the intramural coronary arteries exhibited a histologic pattern similar to that of the epicardial coronary arteries. It is concluded that the exposure of major epicardial coronary arteries to cryoinjury during cold cardioplegic arrest should be avoided where possible.

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Since cryoablation became part of the surgical armamentarium to treat cardiac arrhythmias [1, 2], a rapidly growing literature has been witnessed on histopathologic and electrophysiologic characteristics of cardiac cryolesions, factors contributing to cryogenic effects, and adverse effects. Studies of early and late cryogenic effects on the coronary arteries have been prompted by concern over the possible detrimental results. Several reports deal with the reaction of the epicardial coronary vessels to cryolesions created under normothermic conditions [3-7]. With one exception [4], no or only mild untoward effects were reported in these experimental studies. Clinically, cryoablation of subendocardial, intramural, and subepicardial anatomic substrates of ventricular tachycardia is generally performed under cold cardioplegic arrest. Therefore, a more severe cryoinjury can be expected [8, 9]. This is supported by the more severe intimal hyperplasia and coronary artery stenosis after freezing during cold cardioplegic arrest in the single study in which the long-term effects of cryolesions produced during cold cardioplegic arrest and normothermia are described [5].

In the present study we investigated the short-term and long-term effects of large transmural cryolesions created in the inferior left ventricular wall during cold cardioplegic arrest on epicardial and intramural coronary arteries in dogs.

Material and Methods

Twenty-two mongrel dogs with a weight between 20 and 31 kg were enrolled in the study. All animals received

humane care in compliance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research and the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH publication No. 85-23, revised 1985).

Experimental Procedure

A left lateral thoracotomy was performed under high-dose sufentanil anesthesia and controlled ventilation. During extracorporeal circulation and moderate hypothermia (24°C), cold cardioplegic arrest was induced with St. Thomas' Hospital cardioplegic solution No. 2 (4°C), infused into the aortic root. Ringer's lactate (4°C) was used for continuous topical cooling. The interventricular septal temperature was monitored and did not exceed 18°C during aortic cross-clamping. The mean cross-clamp time $\pm$ standard deviation was 39 ± 7 minutes. A 15-mm cryoprobe (Frigitronics Inc, Shelton, CT), cooled to -70°C for 3 minutes by expanding nitrous oxide, was used to apply two to four epicardial cryolesions and two to four endocardial cryolesions (through the mitral orifice) in the inferior left ventricular wall at the site of the posterior papillary muscle. This resulted in a transmural lesion with a mean epicardial lesion area $\pm$ standard deviation of $10.4 \pm 1.8 \text{ cm}^2$. In small dogs particularly, a 5-mm and a 15-mm probe were used for endocardial freezing. The cryolesion included at least one large ventricular branch of the circumflex coronary artery.

Six dogs were allowed to survive for 6 hours, 2 dogs for 2 days, 3 dogs for 1 month, 5 dogs for 3 months, and 6 dogs for 6 months. Anticoagulants and platelet aggregation inhibitors were not given.

Pathologic Examination

At the end of follow-up, all dogs were sacrificed by an overdose of anesthetic, and the hearts were excised im-

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mediately and examined macroscopically. The area containing the cryolesion was identified. One tissue block, which included at least one large posterolateral branch of the circumflex coronary artery, was excised from the cryolesion. A second tissue block, which included a segment of the left anterior descending coronary artery, was removed from the anterior left ventricular wall at a comparable level and served as control. These tissue blocks were oriented so that cross-sections of the epicardial coronary arteries would be obtained. The heart was transversely sectioned in 1-cm-thick slices. The presence of myocardial lesions distal to the cryolesion was examined. In addition, four transmural tissue blocks were taken from the cryolesion and from the anterior left ventricular wall at a comparable level (for control). The tissue blocks were fixed in 10% buffered formaldehyde and processed by routine histologic techniques for light microscopy. Serial sections (5 μ m thick) were cut and stained with hematoxylin and eosin, elastin van Gieson, and Masson trichrome. Six sections of each tissue block were studied. Representative specimens were fixed in Karnovsky's solution for plastic embedding techniques.

Results

At all follow-up intervals, the epicardial and intramural coronary arteries in the control specimens taken from the anterior left ventricular wall were unremarkable. No lesions distal to the cryolesion were found in the left ventricular wall in any of the dogs.

At 6 hours after cryothermic exposure ($n = 6$), light microscopic examination of the posterolateral branch of the circumflex coronary artery revealed no morphologic changes in 3 of 6 dogs. Subintimal edema and hemorrhage were observed in the remaining 3 animals. In addition, a mild degree of inflammation of the coronary media was found in 2 cryolesions. No thrombi were observed in any of the 6 examined arteries.

Forty-eight hours after operation ($n = 2$), both hearts studied showed edematous changes in the subintimal layer and a mild degree of medial inflammation of the posterolateral branch exposed to cryothermic injury. In addition to the presence of edema and inflammation, 1 of these animals showed a recent thrombus in the injured artery (Fig 1). The other dog showed a mural thrombus in a major coronary vein in the exposed area. Furthermore, mild fragmentation of the internal elastic lamina was seen in 1 animal.

At 1-month follow-up ($n = 3$), stenosis mainly due to concentric intimal hyperplasia was detected in 2 of 3 dogs. Additionally, there was thrombotic occlusion of the arterial lumen with some degree of recanalization in all 3 animals (Fig 2).

At 3 months after freezing ($n = 5$), the coronary artery intima showed severe hyperplasia in all 5 dogs (Fig 3). In 1 dog, the intimal hyperplasia was concentric. In addition, the posterolateral branches showed almost complete occlusion by partially recanalized thrombi in 4 dogs.

At 6 months postoperatively ($n = 6$), the posterolateral branches in the cryolesion showed severe concentric as

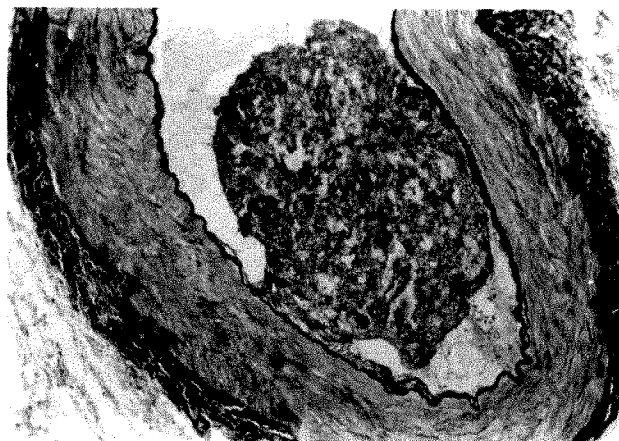


Fig 1. Photomicrograph of a posterolateral coronary arterial branch 48 hours after cryogenic injury, showing recent thrombus. (Elastin van Gieson; $\times 100$ before 52% reduction.)

well as eccentric intimal hyperplasia and virtually complete occlusion by organized thrombi in all 6 animals (Fig 4). In 1 specimen, fragmentation of the internal elastic lamina was noted.

At all follow-up intervals, the intramural coronary arteries in the cryolesion showed histologic alterations similar to those in the epicardial coronary arteries. The diameter of the epicardial coronary arteries, however, was 1.2 ± 0.4 mm, whereas the diameter of the intramural coronary arteries was generally smaller (maximal diameter, 0.8 mm). Nonetheless, some of the intramural coronary arteries involved in the cryolesion remained patent although their lumen was compromised by intimal hyperplasia and thrombosis at 1, 3, and 6 months postoperatively. The light microscopic observations of the myocardium surrounding the intramural coronary arteries at the cryolesion site at various follow-up intervals were as follows. At 6 and 48 hours, interstitial edema and widespread interstitial hemorrhage were present. In addition, at 48 hours transmural necrosis of the ablated myocar-

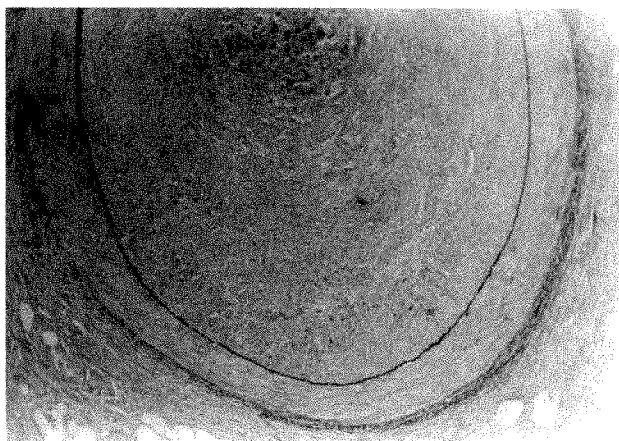


Fig 2. Photomicrograph of a posterolateral branch of the circumflex artery completely occluded by a partially organized thrombus 1 month after freezing. (Elastin van Gieson; $\times 100$ before 52% reduction.)

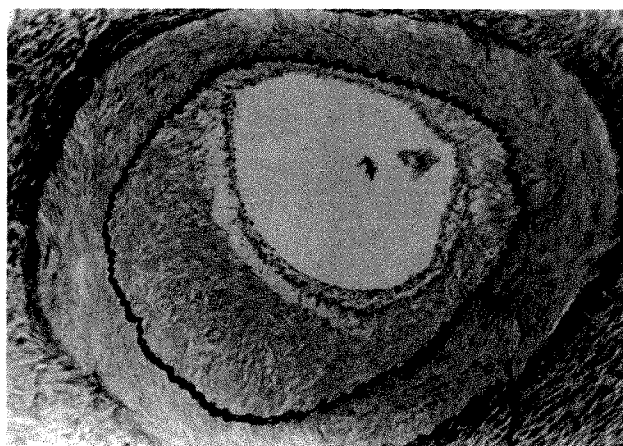


Fig 3. Example of eccentric intimal hyperplasia in a posterolateral epicardial coronary artery demonstrating 65% stenosis of the lumen 3 months after freezing injury. (Elastin van Gieson; $\times 100$ before 52% reduction.)

dium and infiltration with segmented neutrophilic granulocytes were observed. Light microscopic examination at 1 month showed fibrosis at the lesion margin, whereas the center of the lesion still consisted of necrotic myocardium. At 3 and 6 months, the entire lesion was scarred. Changes of the intramural coronary arteries were not related to their location in the cryolesion.

Comment

In 1948, Hass and Taylor [3] were the first to describe the effects of cryoinjury on the myocardium and epicardial coronary arteries. Since then, there have been relatively few reports dealing with the effects of freezing on the coronary arteries [4-7]. The paucity of reports is the more conspicuous if one takes into account the many factors that play a role in the final outcome of hypothermal exposure. A review of the literature on the effects of cryogenic injury shows that the intensity of the injury,

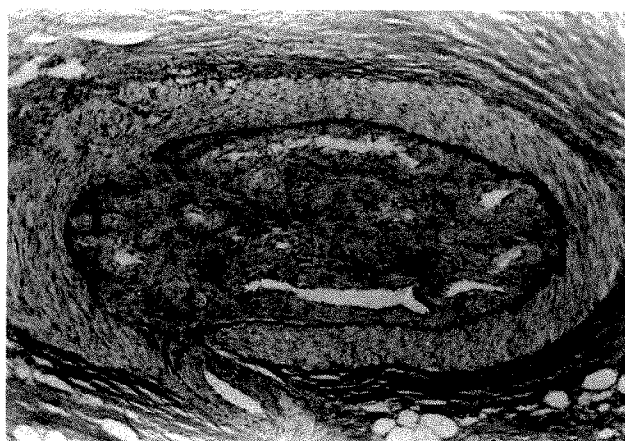


Fig 4. Characteristic histologic appearance of an epicardial posterolateral coronary artery 6 months after cryothermic exposure, demonstrating complete occlusion by organized thrombus. (Elastin van Gieson; $\times 100$ before 52% reduction.)

and hence the structural alterations of the artery, are mainly dependent on the rate of cooling, the depth of cooling, the duration at low temperature, the rate of thaw, the number of successive cooling cycles, and the size of the exposed artery [4-12].

Generally, minimal morphologic alterations of the epicardial coronary arteries have been described in studies on the effects of freezing under normothermic conditions [3, 5-7]. An exception is the study of Mikat and co-workers [4]. They described partial (50%) to complete thrombotic occlusion of the lumen of small and medium-sized coronary arteries in dogs 1 week after freezing. This was followed at 1 month by an increase in mural fibrosis and intimal plaque formation. Also, recanalized thrombi were seen. At 8 to 12 weeks, plaques were still present, but the degree of fibrosis decreased. The lumen of the large and medium-sized coronary arteries, however, remained patent. Cryolesions were applied using a 5-mm probe, cooled to -50°C for 90 to 120 seconds. Two successive cooling cycles were used, which probably explains the more detrimental effects on the coronary arteries.

Holman and associates [5] reported 10% to 60% stenosis of the distal left anterior descending coronary artery in dogs 6 months after cryothermic exposure. Cryolesions were produced with a 4-mm probe cooled to -60°C for 3 minutes. This is the single study on the long-term effects on the epicardial coronary arteries of freezing during cold cardioplegic arrest. Coronary artery stenosis was due to intimal hyperplasia, which was concentric in 2 of 4 dogs. In 1 dog only, the coronary artery was normal. In addition, two small diagonal branches showed 80% stenoses, illustrating the importance of vessel size. The major coronary artery branches remained patent. No morphologic alterations of the coronary arteries were seen in the same study after freezing during normothermia.

The present study provides further evidence for severe cryogenic injury to the coronary arteries when freezing is performed under cold cardioplegic arrest. The histologic picture at 1, 3, and 6 months was dominated by thrombosis and partial recanalization. Also, eccentric as well as concentric intimal hyperplasia were observed. The latter excludes that organized thrombi were the only cause of intimal hyperplasia. In contrast to the study results of Holman and associates [5], most of the major coronary arteries (1.2 ± 0.4 mm in diameter) were almost completely occluded. The presumably longer aortic cross-clamp time (mean, 39 minutes) in our study may have been responsible for the more serious morphologic alterations of the epicardial coronary arteries. The rate of thaw is extremely slow during the period of cross-clamping. The intramural coronary arteries involved in the lesion exhibited similar changes to the epicardial coronary arteries. The fact that the intramural coronary arterial changes were also observed at an early stage suggests that they resulted directly from cryogenic injury rather than being secondary to fibrosis of the lesion [13]. The observed serious intramural coronary artery alterations warrant caution even when cryolesions are applied endocardially, because these lesions have been reported to extend trans-

murally [14, 15]. Further studies are needed on the effects on the epicardial coronary arteries of large endocardial cryolesions applied during cold cardioplegic arrest. Research is required also to evaluate whether administration of antithrombotic agents may prevent or mitigate the occurrence of coronary artery thrombosis due to cryosurgery.

The absence of myocardial lesions distal to the cryolesion does not imply functional capability of the coronary artery exposed to freezing, because of the presence of an extensive coronary artery collateral blood supply in the dog [16], and should therefore not detract from the potential risks of stenosis and occlusion of epicardial coronary arteries in humans.

Although cryoablative methods greatly contribute to the management of both supraventricular and ventricular tachyarrhythmias, the risk of coronary artery occlusion reported herein should be taken into account when clinical application of cryolesions encompassing major coronary arteries is considered, particularly when these arteries supply viable myocardium.

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Improved Tracheal Allograft Viability in Immunosuppressed Rats

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Airway ischemia has been a common cause of morbidity and mortality in clinical lung transplantation. The present study examined the effects of cyclosporin A (CsA) and methylprednisolone (MP) on the viability of the devascularized trachea after heterotopic transplantation and omentopexy. Thirty-six tracheal segments were harvested from 18 donor Lewis rats, wrapped in omentum, and heterotopically implanted into the abdomen of recipient rats. Tracheal segments were randomly allocated into one of six recipient groups ($n = 6$): Lewis syngeneic controls, and five groups of Brown Norway recipients, receiving either no treatment, CsA alone ($5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ or $15 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$), or CsA in combination with MP ($5 \text{ mg CsA} + 1 \text{ mg MP per kg/day}$ or $15 \text{ mg CsA} + 2 \text{ mg MP per kg/day}$, respectively). After

14 days, the tracheal segments were histologically evaluated. Epithelial thickness and the degree of epithelial regeneration were significantly different ($p < 0.05$) between the syngeneic control group and the untreated Brown Norway group. Without immunosuppression there was virtually no epithelium, whereas low-dose immunosuppression yielded intermediate viability, and with high dose CsA and MP we observed improved tracheal viability. In this high-dose group, the epithelium was thicker than in even the syngeneic control group. These results indicate that, in heterotopic tracheal allografts, viability may be improved with an optimum combination of CsA and MP.

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In the last decade, lung transplantation has become a viable option for patients with end-stage pulmonary disease [1]. Improved strategies of allograft preservation and surgical technique have resulted in improved success rates after single- and double-lung transplantation [2]. In the early experience of many centers, bronchial anastomotic complications secondary to ischemia were major causes of morbidity and mortality [3, 4].

Without surgical reconnection of the bronchial circulation, the donor bronchus is at risk of ischemia until local tissue revascularization can be achieved. This process can take 12 to 15 days [5] but can be accelerated by bronchial omentopexy. In the interim, the bronchus is dependent on retrograde collateral perfusion from the pulmonary circulation. Parenchymal pulmonary pathology (eg, rejection, infection, or poor preservation) may decrease pulmonary to bronchial collateral flow. In addition, rejection directed against the bronchus itself may also impair the ingrowth of new vessels from surrounding tissues. Thus, avoidance of rejection in the early postoperative period may be important in preventing ischemic complications of the airway.

Corticosteroids have been employed widely as potent immunosuppressive agents. Previously most programs avoided the routine use of corticosteroids during the early postoperative period because of the negative impact of these agents on bronchial anastomotic healing [6, 7]. It

has also been assumed that steroids would impair neovascularization, yet a number of programs [8], including our own [9], have recently determined that early routine corticosteroid use is, in fact, associated with improved airway healing.

In this study, we examined the role of methylprednisolone (MP) and cyclosporin A (CsA) on the epithelial viability of heterotopic tracheal allografts.

Material and Methods

The heterotopic tracheal transplant model with omentopexy [10] was employed using a technique modified for rats [11]. All experiments were performed on male (250 to 300 g) inbred Lewis rats (Charles River Canada Inc, St-Constant, PQ, Canada) and Brown Norway rats (Harlan Sprague Dawley Inc, Indianapolis, IN). Thirty-six Lewis tracheal segments were harvested and implanted into the omentum of 6 Lewis rats and 30 Brown Norway rats. Animals were randomly allocated into experimental groups, as summarized in Table 1. All animals received humane care in compliance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research, the "Guide for the Care and Use of Laboratory Animals" prepared by the National Academy of Science and published by the National Institutes of Health (NIH publication No. 85-23, revised 1985), and the "Guide to the Care and Use of Experimental Animals" formulated by the Canadian Council on Animal Care. The experimental protocol was approved by the Animal Care Committee of The Toronto Hospital.

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Table 1. Experimental Design

Group	n ^a	Donor	Recipient	Cyclosporine ^b (mg · kg ⁻¹ · day ⁻¹)	Prednisolone ^b (mg · kg ⁻¹ · day ⁻¹)
1	6	Lewis	Lewis	...	...
2	6	Lewis	BN	...	...
3	6	Lewis	BN	5	...
4	6	Lewis	BN	5	1
5	4	Lewis	BN	15	...
6	4	Lewis	BN	15	2

^a Number of animals that survived all 14 days. ^b All doses were given daily subcutaneously, beginning 1 day preoperatively through 14 days postoperatively.

BN = Brown Norway.

Donor Procedure

Lewis rats received heparin (500 UI/kg intraperitoneally) and sodium pentobarbital (65 mg/kg intraperitoneally). In a sterile fashion the trachea was exposed to its bifurcation and a 3.0-cm or greater length was excised and flushed with 10 mL of isotonic saline solution. The trachea was then stretched *ex situ* to its original length and attached to two metal stretchers (U shaped, no. 4 surgical stainless steel wire, 22 gauge; Ethicon, Peterborough, Ont, Canada) and divided into two 1.4-cm lengths (one upper and one lower tracheal segment) for implantation into two recipients.

Recipient Procedure

Brown Norway rats were anesthetized in an induction chamber with halothane (3%) followed by continuous anesthesia with 2% to 3% halothane in oxygen with spontaneous ventilation. After an upper midline abdominal incision, the stretched tracheal segment was wrapped in greater omentum and then secured with two 6-0 Prolene (Ethicon) stitches. The peritoneum and abdominal musculature were closed with 5-0 Prolene interrupted sutures, and the skin was closed with staples.

Drug Administration

Cyclosporin A (Sandimmune IV; Sandoz Canada Inc, Dorval, PQ, Canada) was diluted to 10 mg/mL with castor oil and MP (Solu-Medrol; Upjohn Canada, Don Mills, Ont, Canada) was diluted in sterile water to 2 mg/mL. These were freshly prepared before use and injected subcutaneously daily, beginning 1 day before the operation. No antibiotics were given.

Sacrifice Operation

After 14 days recipient rats were anesthetized in an induction chamber with halothane (3%), followed by continuous anesthesia with halothane (2% to 3%) in oxygen with spontaneous ventilation. Using a lateral abdominal incision, the tracheal segment, wire stretcher, and surrounding omentum were excised and fixed in 5% acetic acid/95% methanol. The animal was then exsanguinated.

Histologic Assessment

We attempted to quantify the viability of the heterotopic allografted trachea by measuring epithelial thickness and

by subjectively assessing and evaluating the epithelial and submucosal histology. Microscopic slides were made from longitudinal sections of the trachea and adherent omentum and stained with hematoxylin and eosin. Assessment was performed by two blinded observers in the following manner.

EPITHELIAL THICKNESS. Four areas between the cartilaginous rings were chosen randomly in the center of the longitudinal segments. Length and area of the epithelium were independently measured, and epithelial thickness was calculated (thickness = area/length). Computer-assisted morphometry was employed, using an MTI-65 camera (DAGE-MIT, Michigan City, IN), Leitz Colourlux K microscope (Leitz, Wetzlar, Germany), and MultiSync 3D videoscreeen (NEC Information Systems, Boxborough, MA) connected to a HiPad Digitizer pad (Houston Instruments, Austin, TX) via a NEC Powermate 386/20 computer with Bioquant IV morphometry software (R & M Biometrics, Nashville, TN).

EPITHELIAL REGENERATION. The epithelium was assessed according to an established grading system [11] as follows: 0, no epithelium, single nonconfluent epithelial cells; 1, confluent single layer nonciliated epithelium; 2, confluent multilayer nonciliated epithelium; and 3, normal mucociliary epithelium.

Statistical Analysis

All data are presented as mean and standard error (SEM). Statistical analysis was performed using the SAS software package (SAS Institute, Cary, NC). If an overall *F* test was significant in an one-way analysis of variance, selected comparisons were performed between treatment groups and two control groups—syngeneic transplants and untreated allografts. A treatment effect was declared to be significant at the 5% level.

Results

Thirty-six rats underwent tracheal implantation with an operative survival of 100%. Four animals treated with high-dose CsA (15 mg · kg⁻¹ · day⁻¹) died within 7 days with widespread intraabdominal infection (2 in both the with and without MP groups [groups 5 and 6]); these animals were excluded from our analysis. Macroscopically, rats treated with MP were grossly distinguishable from those not receiving steroids. In steroid-treated animals reduced inflammation and fewer peritoneal adhesions were noted at sacrifice 14 days postoperatively.

The thickness of the tracheal epithelium was found to be significantly less in the two groups (groups 2 and 3) with the lowest levels of immunosuppression than in the Lewis to Lewis syngeneic control animals (Fig 1). Epithelial thickness in the intermediate immunosuppression allograft groups (groups 4 and 5) was not significantly different from syngeneic controls. Interestingly, in the 4 surviving animals treated with both high-dose CsA and high-dose MP (group 6), the epithelial thickness was increased and significantly thicker even than in syngeneic controls.

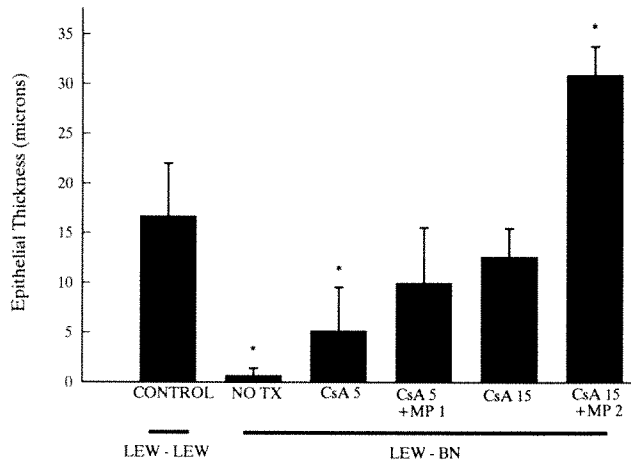


Fig 1. Average epithelial thickness in heterotopic tracheal isografts or allografts with or without immunosuppression. Data are presented as mean $\pm$ standard error. (BN = Brown Norway; CsA = cyclosporin A; LEW = Lewis; MP = methylprednisolone; TX = treatment; * $p < 0.05$ when compared with syngeneic controls.)

The epithelial regeneration assessment demonstrated almost complete destruction of the epithelium after allografting without immunosuppression (Fig 2). Note that even at 14 days, the epithelium is not morphologically normal (a regeneration score of 3 is considered normal) in syngeneic transplants. Compared with syngeneic controls, untreated allografted animals had a significantly lower regeneration score. Similar to the thickness data, group 6, with the highest level of immunosuppression, had a significantly higher regeneration score compared with syngeneic controls. Only in this group has the epithelium returned to normal. There were no significant differences in regeneration score in the intermediate immunosuppression groups. Figure 3 illustrates three typical examples of regeneration after allotransplantation.

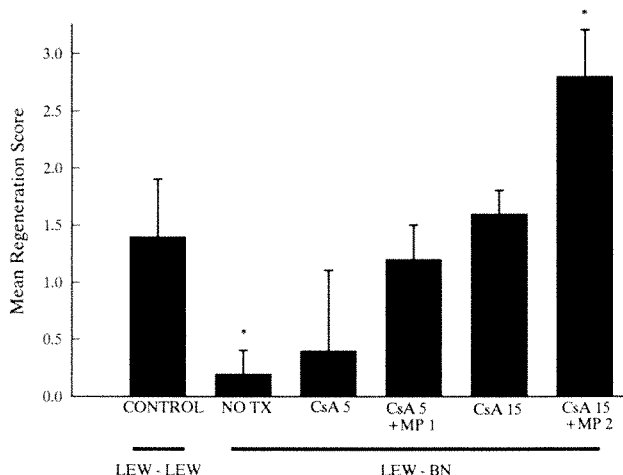


Fig 2. Average epithelial regeneration score in heterotopic tracheal isografts or allografts with or without immunosuppression. Data are presented as mean $\pm$ standard error. (* $p < 0.05$ compared with syngeneic controls; abbreviations are as in Figure 1.)

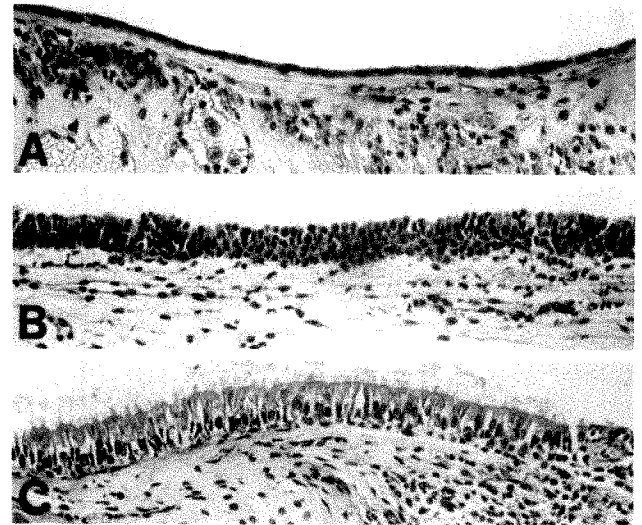


Fig 3. Representative examples of tracheal epithelium. (A) Lewis trachea implanted into Brown Norway recipient without immunosuppression. Only a monolayer of epithelial cells is present. (B) Lewis trachea implanted into Lewis recipient without treatment. The epithelium is made up of several layers of nucleated cells but cilia are not present. (C) Lewis trachea implanted into Brown Norway recipient treated with cyclosporin A, $15 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$, and methylprednisolone, $2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$. Virtually normal epithelium with basal nuclei and ciliated cells is seen.

Comments

Before the first successful clinical lung transplantation in 1983, bronchial anastomotic complications contributed directly to the death of most patients surviving more than 10 days after the operation [12]. The early success of the Toronto lung transplantation program may have been in part due to the routine use of bronchial anastomotic omentopexy. Earlier revascularization of the donor bronchus and enclosure by omentum of partial anastomotic dehiscence were powerful arguments for using omentopexy routinely. Yet, even with omentopexy, bronchial anastomotic complications proved to be a major cause of morbidity and mortality [3].

In the past, corticosteroids were avoided in the early postoperative period because of evidence in canine auto-transplantation models that such therapy resulted in impaired bronchial healing [6, 7]. Recently, however, a number of programs, including our own, have followed the lead of the San Antonio group [3] and employed corticosteroids routinely during the posttransplantation period with excellent results.

In the present study, we attempted to quantify viability of a heterotopic tracheal allograft by making quantitative and qualitative assessments of the epithelium. We have previously shown these measures to correlate with a direct measurement of tracheal vascularity [11]. In this study we did not directly measure tracheal vascularity. Here, we demonstrated that uncontrolled rejection significantly impairs the regeneration of the tracheal epithelium. Immunosuppression, on the other hand, allows regeneration to occur. We found improved tracheal via-

bility in high-dose CsA groups with or without MP compared with the untreated group.

An unexpected finding was the improved tracheal viability in group 6 (high-dose CsA and high-dose steroid). In this group, the tracheal epithelium was even thicker and the morphology more normal than in the syngeneic control group. Possible explanations for this observation include a reduction in peritracheal inflammation with improved angiogenesis or a direct trophic effect on the tracheal epithelium.

Corticosteroids have been shown to have antiangiogenic properties that vary greatly between steroid molecules. For example, dexamethasone has minimal angiogenic effects compared with cortisone [13]. In this model of heterotopic tracheal allotransplantation, viability was observed to be improved with a high dose of CsA and MP after omentopexy. Whether steroid therapy alone (without cyclosporine) would have the same effect is not known. However, this cyclosporine-corticosteroid combination regimen was chosen because it mimics that employed in most clinical lung transplant programs.

The epithelial regeneration scoring system used in this study is based on descriptions of repair after mechanical and toxic injury to rat and hamster trachea [14, 15]. Previous work has shown that the regeneration of epithelium after devascularization and syngeneic heterotransplantation is not completed by 14 days [11]. In this study we confirmed that the epithelial morphology has not returned to normal by this time. Fourteen days, however, was found to be sufficient time for the development of a strong immune response, as evidence of early rejection was apparent histologically in the allografted study groups by this time. The possibility exists that the epithelium had regenerated but was subsequently destroyed by rejection in the allogenic groups not given high-dose immunosuppression.

The heterotopic rat tracheal transplant model offers the advantages of simplicity, controlled MHC disparities, and low cost. It allows the evaluation of tracheal viability, independent of the complexities of pulmonary to bronchial retrograde circulation. On the other hand, such an avascular graft may be less susceptible to rejection than bronchial tissue included in a pulmonary allograft. It also requires the implantation of a foreign body (wire "stretchers") into the abdominal cavity. We have found these stretchers necessary to prevent the natural retraction of the trachea wall between cartilaginous rings [11].

Prophylactic antibiotics were not administered in this study. Despite sterile surgical technique, 2 rats in each of the groups receiving high-dose CsA died with intraabdominal sepsis. The dose administered to these animals was chosen arbitrarily to minimize acute rejection. It exceeds the current dosage used in human lung transplantation. It is interesting that the addition of high-dose corticosteroid was not associated with a higher incidence of intraabdominal sepsis.

In conclusion, in this model of heterotopic tracheal allotransplantation with omentopexy without any immunosuppression, there was poor tracheal viability as determined by epithelial thickness and subjective histological

assessment. Low-dose CsA ($5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$) and MP ($1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$) result in similar tracheal viability to syngeneic controls. High-dose immunosuppression (CsA, $15 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$, and MP, $2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$) produced improved tracheal viability in comparison with syngeneic controls.

After allografting, the prevention of rejection with adequate immunosuppression is necessary to allow successful regeneration. Specifically, the addition of corticosteroids does not appear to impair regeneration.

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Argon Beam Coagulation Compared With Cryoablation of Ventricular Subendocardium

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The Argon Beam Coagulator uses radiofrequency energy to excite argon gas that may be used for ventricular ablation. The effects of power level and number of applications of the Argon Beam Coagulator were compared with cryothermia. Ten mongrel dogs underwent cardiac extirpation. The endocardial surfaces of 5 hearts were used for the creation of lesions using the Argon Beam Coagulator at five power levels with either one or two applications. Five hearts were used for endocardial and epicardial lesions using cryothermia (15-mm-diameter probe at -70°C) for 1, 2, 3, or 4 minutes. The Argon Beam Coagulator lesions showed an increase in depth with increasing power levels (2.25 ± 1.05 mm at 50

W to 6.64 ± 0.75 mm at 150 W) and number of applications (maximum depth of 6.64 ± 0.75 mm with one application, 11.2 ± 1.1 mm with two applications). Cryothermia lesions were similar in depth regardless of duration or site of application (range, 6.1 to 10.2 mm). Both techniques resulted in homogeneous and well-demarcated lesions. These data show that the Argon Beam Coagulator results in discrete endocardial lesions, which may be created quickly and reproducibly. This may be a useful alternative for the operative ablation of endocardial scar in the treatment of ventricular tachycardia.

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There are numerous methods that are currently used for the surgical treatment of drug-refractory ventricular tachycardia. These include subendocardial resection [1-4], cryothermia [5-9], laser ablation [10, 11], left ventricular aneurysmectomy, and placement of antitachycardia/cardioverter/defibrillator devices [12, 13]. For patients in whom endocardial scar is suggested as the substrate for macroreentry for the initiation of ventricular tachycardia, subendocardial resection with cryosurgery has become the most popular open heart procedure. Although it has a relatively good success rate [2, 3, 14], the creation of cryolesions can be time-consuming and, due to their circular geometry, may leave gaps between lesions [15].

The Argon Beam Coagulator (ABC) (System 6000 Electrosurgical Generator; Birtcher Medical Systems, Inc, Irvine, CA) is a radiofrequency isolated electrosurgical generator [16]. It uses a coaxial, laminar flow of argon gas to enhance coagulation, which results in increased control and efficacy of coagulation. The device has a nozzle that must be held 1 cm or less above the tissue to be coagulated, and it may be moved in a "painting" motion over the desired area. The main advantages are that the ABC may be applied quickly, allows application to areas that may be difficult to reach using other techniques, and produces a visible lesion so as to prevent skip areas.

This system, in addition to subendocardial resection, has been used successfully at Duke University Hospital in 12 patients with medically refractory ventricular tachycardia to ablate endocardial scar tissue associated with ar-

rhythmogenesis. The purpose of this study was to characterize the lesions created by the coagulator and compare them with lesions produced by cryothermia.

Material and Methods

Ten adult dogs were anesthetized using pentobarbital (30 mg/kg), intubated, and ventilated using a Harvard respirator. All animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH publication No. 85-23, revised 1985). An unperfused model was selected whereby a median sternotomy was performed and hearts were rapidly excised. The atria were removed and the right ventricle was dissected off the left ventricle and septum. The left ventricle was opened with an incision through the septum, and the endocardial surface was exposed completely to give a rectangular block of myocardium. In 5 animals, the ABC was used to create endocardial lesions. A template with ten openings, each measuring 1×1 cm, was placed over the endocardium. The ABC was used to create lesions by passing the hand piece and nozzle over the individual openings at a rate of approximately 1 cm/s. Several passes were made over the opening until the tissue was completely ablated. Several lesions were created at different power settings: 50, 75, 100, 125, and 150 W with either one or two complete applications to each block. Therefore, a total of 50 lesions were created.

In 5 other animals, cryolesions were created using hearts excised in the same fashion as above. A heating pad was placed under the myocardium and set at 37°C to act as a heat sink. The endocardial surface was used first

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Table 1. Argon Beam Lesion Depth^a

Application Frequency	Power Level (W)				
	50	75	100	125	150
1	2.25 ± 1.05	1.65 ± 0.05	2.36 ± 0.93	5.09 ± 0.64	6.64 ± 0.75
2	3.3 ± 1.6	3.83 ± 2.1	7.78 ± 2.1	11.03 ± 2.2	11.2 ± 1.1

^a Depth of lesion (mm) created by Argon Beam Coagulator at different power levels using either one or two applications performed at a rate of approximately 1 cm/s. (Mean ± standard error of the mean.)

to create lesions using a 15-mm cryoprobe (Frigitronics Inc, Shelton, CT). Several lesions were created by placing the probe on the heart and cooling to -70°C for either 1, 2, 3, or 4 minutes. The tissue was turned over to expose the epicardial surface, on which the cryoprobe was placed again for 1, 2, 3, or 4 minutes. Eight lesions were created for each heart for an overall total of 40.

Once the lesions were produced, the hearts were tacked onto cork boards and placed in 10% formalin solution. Once adequately fixed, the lesions were excised from the myocardial slabs and dehydrated through graded ethanols followed by embedding in paraffin on a Tissue-Tek VIP 3000 (Miles Scientific, IL) automatic embedding apparatus. Thin sections (6 μm) were cut on a microtome and stained with Verhoeff-van Gieson-Masson modified connective tissue stain. The sections were then assessed by light microscopy, and depths were measured using a computer-assisted image analysis system (Videometric System 150; Innovision, San Diego, CA).

Argon beam coagulator data were assessed using linear regression analysis (SAS Institute, Cary, NC). Cryolesions were compared at different times using analysis of variance. A *p* value of 0.05 was considered indicative of statistical significance.

Results

A total of 10 dogs weighing 24.85 ± 1.3 kg were used. In the ABC group, 5 hearts received 50 lesions, of which 39 were acceptable for histological examination. Eleven samples showed surface disruption as a result of fixation and preparation and therefore were not acceptable to measure lesion depths. The lesion depths for the different power outputs and frequency of passes are shown in Table 1. Figure 1 shows the increase in tissue penetration with increasing power and number of passes. Using linear regression, the depth of lesion created by ABC correlated directly with increasing power levels with an *r* value of 0.842 for the single-pass group and 0.82 for the double-pass hearts.

Light microscopy revealed that ABC lesions created using 50 and 75 W with one pass resulted in an intact superficial connective tissue layer consisting of elastic elements and collagen and a few cells along the endocardial surface. At power levels of 100 W and greater, there was a deeply eosinophilic, coagulated myocardial cellular change which increased in thickness with increasing power. All of the double-pass lesions showed dark-staining, carbonized, vacuolated connective tissue layers.

Myocardium had a thicker eosinophilic, coagulated cell layer with marked vacuolization, which was first evident in the 100-W power output lesion. Lesions were generally well-demarcated and circumscribed (Fig 2).

Five hearts were used for the cryolesions with 40 lesions created, of which 30 were useful for microscopic analysis. Rejection of samples was based on surface disruption, inability to determine lesion borders, and improper fixation of tissue. The heart was placed on a heating pad, but it was difficult to maintain constant temperature. Temperatures ranged from 32° to 37°C . The depth of the lesions at the midpoint of the ice ball for the different times of application are shown in Table 2. Analysis of variance revealed that there were no statistically significant differences between the depths of lesions for the different application times using either epicardial or endocardial lesions.

Histological examination showed that the cryolesions had intact surfaces with well-demarcated edges and homogeneous necrosis within the lesions (Fig 3). However, there were several lesions that were difficult to measure due to the application of the probe over an area of

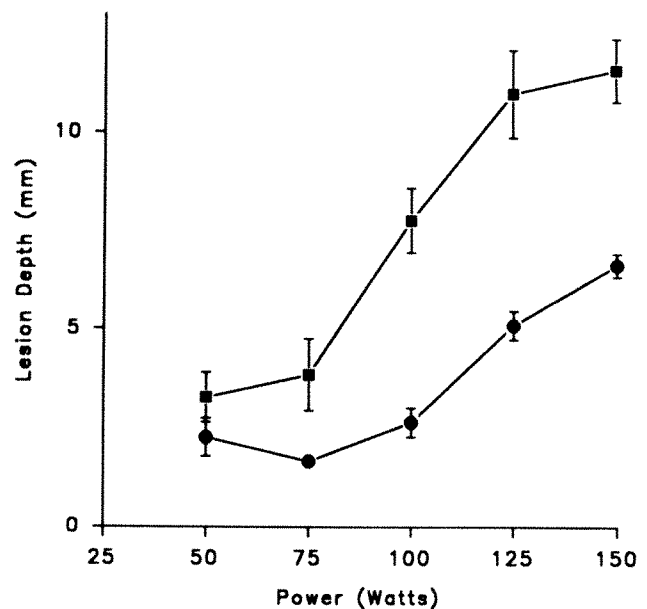


Fig 1. Increasing depth of lesions created with the Argon Beam Coagulator as the power level is elevated. Lesions created with a single application are denoted by the circles; those from a double application are shown by the squares. (Mean ± standard error of the mean.)



Fig 2. Lesion created by the Argon Beam Coagulator at a power setting of 100 W with one application. (Magnification, $\times 6.5$ before 40% reduction.)

trabeculation on the endocardial surface. The trabecula would create pockets and bridges between it and the underlying myocardium, which would make it difficult for the cryoprobe to freeze the myocardium lying below the trabecula uniformly (Fig 4). This lack of uniformity was not seen in the ABC group, presumably because of the directed gas's ability to focus the heat below and around trabeculae.

Comment

In patients with medically refractory reentrant ventricular tachycardia, surgical treatment has proved to be effective. The most common procedures involve subendocardial resection and cryoablation of scar tissue with or without resection of a left ventricular aneurysm. Despite the variability of ventricular function and the substrate for and nature of the dysrhythmias, surgical results have been acceptable, with operative mortality varying between 10% and 20% [3, 14]. Success rates for ablating the dysrhythmias range from 70% to 93% [2, 3, 14].

The operations can often be long and complicated, especially if numerous mapping procedures are performed, a large area of subendocardial resection is required, or many cryolesions must be placed. Cryolesions take 2 to 3 minutes each with an average of 6 to 12 lesions



Fig 3. Lesion created by a 15-mm cryoprobe for 3 minutes on the endocardial surface. (Magnification, $\times 6.5$ before 12% reduction.)

required per case [6] (ie, 12 to 36 minutes). In addition, cryolesions are made usually with circular probes, requiring that lesions be overlapped 2.5 mm to assure complete

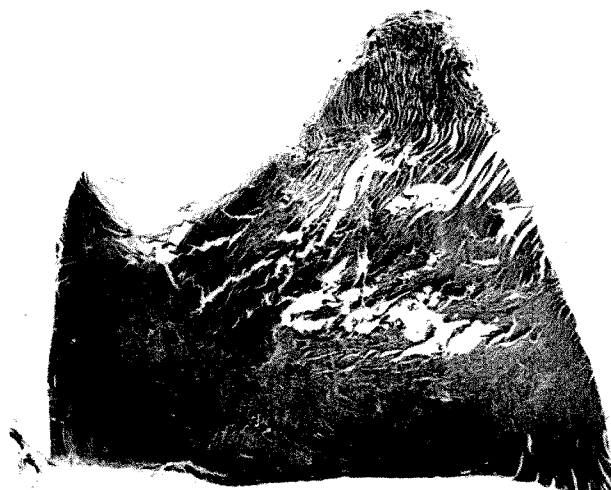


Fig 4. Another lesion created by a 15-mm cryoprobe for 3 minutes, which demonstrates the irregularity of the surface of the endocardium resulting in a variable depth of penetration by the cryoprobe. (Magnification, $\times 6.5$ before 22% reduction.)

Table 2. Cryolesion Depth^a

Site	Duration of Freeze (min)			
	1	2	3	4
Epicardium	6.10 $\pm$ 0.43	6.35 $\pm$ 1.31	6.92 $\pm$ 0.31	6.55 $\pm$ 1.28
Endocardium	7.88 $\pm$ 1.63	9.9 $\pm$ 1.52	7.7 $\pm$ 1.82	10.2 $\pm$ 2.65

^a Depth of lesion (mm) created by 15-mm cryoprobe for different times either on the epicardial or endocardial surface of the canine ventricle. (Mean $\pm$ standard error of the mean.)

coverage [15]. It is therefore possible to have areas where there is inadequate ablation, which may result in a substrate that would support recurrence of the dysrhythmia.

The ABC system uses radiofrequency energy to excite argon gas within a nozzle. The beam then exits the nozzle and spreads evenly over the tissue, heating it to a maximum of 110°C [16]. The excited gas can flow into channels and pockets created by the trabeculation of the ventricle, thereby enabling its application to be more uniform over an irregular surface. This type of ablation may be advantageous because it may be applied more rapidly than cryothermia, resulting in a visible color change of the tissue indicating that an area has been covered. The depth of penetration of the lesion varies depending on the power of the radiofrequency energy and duration of application as shown in this study. In addition, the created lesion appears to be homogeneous and well-circumscribed, which should not support further reentry. In the 12 patients who have received ABC treatment for their ventricular dysrhythmia, there have been no measured adverse effects on ventricular function.

The cryolesions created during this study show that lesion depth may be affected seriously if there are any irregularities of the surface of the endocardium. Most experimental studies assessing cryolesion depth have been performed using only epicardium, which has a smooth surface [15, 17]. Because there are often trabeculated areas of left ventricular endocardium that are cryoablated, this may be another reason for inadequate coverage in addition to failure to overlap lesions.

Previous studies have reported that cryolesion depth is affected by temperature of the tissue and duration of application. This was not well reproduced under our test conditions. In fact, lesions all had similar depths irrespective of duration of cryoablation. This likely reflects the fact that the tissue was not perfused during this study. The maximal cryolesion was created early during the application of the probe. Mikat and associates [18] showed that an average lesion depth of 5 mm was created when the cryoprobe was applied to the epicardium of perfused dog hearts for 90 to 120 seconds. This is less than the 9.9-mm lesion that was created during the same time under our experimental conditions. Perfused tissue likely creates a dynamic heat sink, and therefore it takes longer to create the maximal lesion. Other variables known to affect cryolesion depth are temperature and nitrous oxide tank pressure. Holman and colleagues [17] and Markovitz and co-workers [19] both showed that cryolesions had similar sizes when applied to tissues at 32° to 37°C but deepened as the temperature decreased. Despite maintenance of tissue temperature greater than 32°C using a heating pad in this study, there were no differences in lesion depths. This further suggests that tissue perfusion is an important consideration for the determination of cryolesion depth and not just tissue temperature alone. Long cryothermia sessions can deplete nitrous oxide reserves, resulting in lower tank pressure. At lower tank pressures, lesion volumes can be reduced by 41% [19]. Therefore, the lesion created by cryothermia can be affected by numerous factors.

Creation of endocardial lesions using the ABC system is not without potential problems. First, the movement of the nozzle is completely at the discretion of the operator. Therefore, to assure a reproducible lesion, a constant motion must be practiced. Because the device heats tissue, the operator must be especially careful near valves and chordae to prevent damage of these structures. However, an advantage is its extreme maneuverability and precision of application, which is in contrast to cryothermia. Although this was an acute study, the chronic lesion created by the device is likely to be similar, as has been reported by other groups using other ablation techniques [15, 17]. Unlike experiments using cryothermia [20], this study did not assess the electrical neutrality of the lesions created, but it could be extrapolated from other studies using radiofrequency energy that ablated tissue would be electrically silent after treatment. Although we did not compare the ABC lesions with those created by argon or neodymium:yttrium-aluminum garnet lasers [10, 11], we believe that the ABC system may be as effective as lasers.

This study used a nonperfused animal model for the creation of ABC and cryolesions. The advantages of this model are that it is simple, allows for a large number of lesions to be created per animal heart, and facilitates using endocardium or epicardium as substrate. Perfused models are limited by the number and location of lesions that may be produced and are much more cumbersome to perform. We believe that this model has resulted in the creation of lesions that are reproducible and similar to those produced using other models (with the exception of not being able to show a temperature/time dependence for cryolesions for reasons as outlined). In addition, observations with respect to endocardial cryolesions are important and should be considered when using this technique.

In conclusion, the ABC produces discrete, homogeneous, well-demarcated lesions, the depths of which are controllable by adjusting the power output of the device and the number and duration of applications. It may be a useful adjunct for the treatment of ventricular tachycardia when an open heart procedure is warranted.

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Noncardiogenic Pulmonary Edema Complicating Lung Resection

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Postresectional pulmonary edema is a rare but potentially fatal complication of thoracic operations. In a retrospective study of 402 lung resections we have identified 11 cases of postresectional, noncardiogenic pulmonary edema. We have analyzed the individual data to test recognized hypotheses regarding this condition. Pulmonary edema occurred in 5.1% of right pneumonectomies, 4.0% of left pneumonectomies, and 1% of all lobectomies. In 2 patients the symptoms occurred immediately after operation; in the other 9 the mean interval to diagnosis was 43.4 hours. All 11 patients were in a positive fluid balance in the first 24 hours after operation

(mean, 20.8 ± 9.1 mL/kg). However, there was no significant difference between this value and the respective values for control groups of 20 patients having pneumonectomies and 20 patients having lobectomies in whom pulmonary edema did not develop. Our findings differ from other reported series in that perioperative fluid overload was not found to be a significant contributory factor in the development of postresectional pulmonary edema. We discuss other possible mechanisms for this phenomenon.

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Noncardiogenic pulmonary edema after lung resection is a rare but potentially life-threatening complication. Most thoracic surgeons are aware of anecdotal reports of this condition, but there have been few reviews of large series of patients [1, 2]. The underlying mechanism therefore remains undetermined, and explanations are based largely on animal experimental work [3]. At present noncardiogenic pulmonary edema is thought to comprise an increase in filtration pressure across the alveolar-capillary membrane with a decrease in the lymphatic drainage of the affected lung [1]. There is also evidence for increased permeability of the alveolar-capillary membrane [4]. Significant contributory factors that have been previously identified include the amount of lung tissue resected and a large perioperative fluid load [3]. However, we have observed this condition in patients who have received a comparatively small fluid load. We have therefore reviewed the data on patients who have undergone lung resection since 1983 and have analyzed the details of those in whom noncardiogenic pulmonary edema has developed. We aimed to test the recognized hypotheses regarding this rare condition.

Material and Methods

The records were reviewed of 402 patients who underwent lung resection at Killingbeck Hospital between 1983 and 1991. Pneumonectomy was performed in 205 (79 right

and 126 left), lobectomy in 155, bilobectomy in 30, and wedge resection in 12. Noncardiogenic pulmonary edema was diagnosed on clinical, radiological, or postmortem findings having excluded the following causes: cardiac failure due to myocardial infarction or cardiac arrhythmia, chest infection, aspiration pneumonia, pulmonary thromboembolism, and adult respiratory distress syndrome due to septicemia. Anesthetic and intensive care records were analyzed to calculate the intraoperative fluid load and the fluid balance for the immediate postoperative period. A figure for the net fluid balance in the first 24 hours after operation was derived from the intravenous colloid and crystalloid administration (including intraoperative), intraoperative blood loss (calculated from operating room suction and swab weight), urine output and nasogastric aspiration, and postoperative intercostal drainage. Differences between patients in whom pulmonary edema developed and those in whom it did not were assessed by the Mann-Whitney U test.

Results

Eleven cases of pulmonary edema complicating lung resection were identified (2.7% of all cases), occurring in 5 of 126 (4%) left pneumonectomies, in 4 of 79 (5.1%) right pneumonectomies, and in the contralateral lung in 2 of 197 (1%) lesser resections (155 lobectomies, 30 bilobectomies, and 12 wedge resections). Nine men (3.0% of all male patients) and 2 women (2%) aged 42 to 70 years (mean age, 57.0 ± 8.5 years) were affected. There was a history of cardiovascular disease in 3 patients. Mean preoperative pulmonary function test results were as follows: forced vital capacity, 3.4 ± 0.8 L, and forced expiratory volume in 1 second, 2.2 ± 0.6 L.

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Table 1. Details of Survivors of Postresectional Pulmonary Edema

Patient No.	Sex	Age (y)	Operation	Interval to Symptoms
1	M	42	L pneumonectomy	72 h
2	M	56	L pneumonectomy	48 h
3	M	65	R upper lobectomy	72 h
4	M	63	R pneumonectomy	Immediate
5	M	48	L pneumonectomy	48 h

L = left; R = right.

The mean total intraoperative fluid load for this group was $1,555 \pm 668$ mL (mean colloid, 1,050 mL; mean crystalloid, 607 mL). All patients were in a positive fluid balance for the immediate 24-hour postoperative period (mean, 20.8 ± 9.1 mL/kg body weight). These results were compared with the respective values for two control groups. One group (18 male and 2 female patients; mean age, 62.6 ± 5.4 years) comprised the last 20 consecutive pneumonectomies (13 left, 7 right) performed in this unit. The second group (15 male and 5 female patients; mean age, 61.8 ± 7.0 years) comprised the last 20 consecutive lesser resections (6 right upper lobectomies, 5 left upper, 5 left lower, 3 bilobectomies, and 1 right lower) performed in this unit. One patient in each group had prior evidence of cardiovascular disease. The respective mean values for fluid balance in the immediate 24-hour postoperative period were 15.7 ± 6.4 mL/kg in the pneumonectomy group and 20.5 ± 10.8 mL/kg in the lobectomy group. Using the Mann-Whitney U test, these values were not found to be significantly different from those in patients in whom pulmonary edema developed ($p = 0.81$).

In 2 patients pulmonary edema was recognized immediately after the operation. In the remaining 9 patients the mean onset of symptoms was 43.4 ± 19.9 hours after operation.

Six patients subsequently died, despite mechanical ventilation in all 6 (mean duration, 6.3 ± 3.8 days) at a mean postoperative interval of 14.4 days. Further analysis of those who survived and those who died is presented in Tables 1 and 2. There was no difference between the groups in terms of type of resection, mean age (54.8 versus 58.8 years), mean interval to symptoms (48 ± 29

Table 2. Details of Deaths Caused by Postresectional Pulmonary Edema

Patient No.	Sex	Age (y)	Operation	Interval to Symptoms
1	M	70	R pneumonectomy	12 h
2	M	48	L pneumonectomy	48 h
3	M	59	R upper/middle lobectomy	Immediate
4	F	51	L pneumonectomy	40 h
5	M	58	R pneumonectomy	48 h
6	F	67	R pneumonectomy	15 h

L = left; R = right.

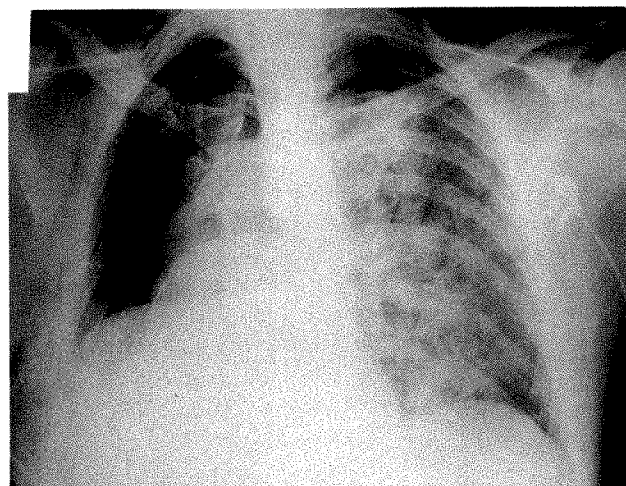


Fig 1. Pulmonary edema developing immediately after right pneumonectomy in a 62-year-old man.

versus 27 ± 21 hours), or cardiovascular disease (1 survivor, 2 who died).

Case Report:

The following case report illustrates the typical clinical findings in postresectional pulmonary edema. A 62-year-old businessman was admitted for right thoracotomy for squamous carcinoma of the bronchus. Preoperative investigations revealed no evidence of ischemic heart disease, and spirometry was good: forced vital capacity, 3.4 L; forced expiratory volume in 1 second, 2.6 L; ratio of forced vital capacity to forced expiratory volume in 1 second, 0.76.

At operation tumor was found to be impinging on the right main bronchus and there was no evidence of lymph node involvement. A standard right pneumonectomy was performed with staple closure of the right main bronchus. The operation lasted 3 hours. Intraoperative blood loss was approximately 500 mL, and fluid replacement during this period consisted of 1,000 mL of Hartmann's solution and 500 mL of hydroxyethyl starch.

The patient was extubated at the end of the procedure and began to breathe spontaneously. Within 30 minutes respiratory distress developed and he suffered a respiratory arrest. He required immediate endotracheal intubation and was transferred to the intensive care unit, where he was found to be in severe pulmonary edema (Fig 1) and severely hypoxic: oxygen tension, 6.67 kPa (50 mm Hg); carbon dioxide tension, 7.28 kPa (55 mm Hg). His peak inflation pressure was elevated at 49.6 cm H₂O, and he was fully ventilated on 60% oxygen.

A Swan-Ganz catheter was inserted, and pulmonary artery pressures were found to be elevated (systolic, 42 mm Hg; diastolic, 21 mm Hg), although the pulmonary capillary wedge pressure was low at 4 mm Hg. Cardiac output (measured by thermodilution) was 5.8 L/min.

A diuresis of 800 mL was induced over the next 6 hours by intermittent boluses of furosemide; pulmonary func-

tion and peak inflation pressures subsequently improved, but attempted extubation was unsuccessful. Continued diuresis was maintained and intravenous fluid administration was limited to 200 mL of salt-poor albumin per day. By the fourth postoperative day peak inflation pressures had fallen to normal, radiographic appearances were resolving, and extubation was successful.

The patient made an uneventful subsequent recovery and was discharged from the hospital 14 days after operation. Serial cardiac enzyme level determinations and electrocardiography revealed no evidence of a perioperative myocardial infarction. Microbial cultures from endotracheal secretions were negative.

Comment

Our findings differ from those of other reported series in that we have found that the development of pulmonary edema after lung resection does not appear to be associated with a significantly excessive perioperative fluid load. We found no significant difference between the perioperative fluid load administered to the patients in whom edema developed and those in whom it did not. The mean positive fluid balance in the first 24 hours after operation in our group in whom edema developed was also lower than that in other reported series [1, 2, 4, 5]. In all of these series fluid overload was thought to be a major cause of pulmonary edema.

Our series of patients differed in some other ways from those in other reports. Although it is rarely reported, we have documented the occurrence of pulmonary edema after lobectomy. Also, unlike other authors [1], we have not found that the side of pneumonectomy is a significant risk factor.

The mechanism of pulmonary edema after lung resection remains undetermined. Two underlying processes are believed to occur: raised capillary hydrostatic pressure and increased capillary permeability. After major lung resection the remaining lung tissue is subjected to an increased pulmonary artery blood flow as the cardiac output is redistributed [1]. As demonstrated in the case report presented here, the mean pulmonary artery pressure increases but the pulmonary capillary wedge pressure is not elevated owing to distention and recruitment of the pulmonary microvasculature and reduction in total pulmonary vascular resistance [6]. Pulmonary capillary wedge pressure may, however, be falsely low owing to a decrease in cardiac output on occlusion of the pulmonary artery caused by acute compromise of the reduced pulmonary vascular bed [7]. Fluid filtration is flow dependent [6], and as the mean capillary pressure rises, the net filtration force increases [1]. The formation of edema is also thought to be accelerated by the reduction in effective lymphatic drainage by lung resection [3]. Perioperative fluid overload compounds the problem by further increasing cardiac output, pulmonary artery pressure, and net filtration.

Evidence for an increase in permeability in postresection edema comes from a report of 5 patients in whom endotracheal aspirates demonstrated an elevated edema fluid: serum protein ratio [4]. There were methodological

problems in that the aspirates may have been contaminated by upper airways secretions, but other evidence exists to favor a change in permeability. Experimental work with isolated perfused dog lobes has demonstrated a disproportionate increase in edema formation with elevated pulmonary venous pressures [8]. This had been previously attributed to a decrease in tissue buffering as the lung became more edematous, but these experiments showed this phenomenon to be independent of tissue hydration. A more likely explanation is that permeability is increased by pressure effects on the alveolar-capillary membrane. There is further experimental evidence that distention may widen the intercellular junctions within the endothelial layer of the alveolar-capillary membrane, facilitating fluid efflux [9]. There is also evidence that the high resistance of the alveolar epithelium (which is up to 10 times less permeable than the endothelium) may suddenly break down under mechanical stress, ie, fluid distention [10, 11].

Why pulmonary edema develops in some patients after lung resection despite relatively little fluid load and comparatively little reduction in effective lymphatic drainage (ie, after lobectomy) remains unknown. However, the underlying mechanism may be damage to the alveolar-capillary membrane. A transient increase in postoperative pulmonary capillary pressure, which is already elevated, may be sufficient to widen or damage intercellular junctions, causing subsequent fluid efflux. Possible causes of a sudden increase in pressure include release of endogenous catecholamines in response to pain and reflex pulmonary vasoconstriction in response to transient hypoxia.

Further study into the mechanism of pulmonary edema after lung resection is clearly required. It is not satisfactory to attribute the effects to perioperative fluid overload alone. Investigations into the changes in permeability of the alveolar-capillary membrane during and after lung resection should be performed.

We thank Mr N. R. Saunders and Mr D. R. Walker, Consultant Cardiothoracic Surgeons, for their permission to report their cases.

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Notice From the American Board of Thoracic Surgery

The American Board of Thoracic Surgery began its recertification process in 1984. Diplomates interested in participating in this examination should maintain a documented list of the operations they performed during the year prior to application for recertification. This practice review should consist of 1 year's consecutive major operative experiences. (If more than 100 cases occur in 1 year, only 100 need to be listed.) They should also keep a record of their attendance at approved postgraduate medical education activities for the 2 years prior to application. A minimum of 100 hours of approved CME activity is required.

In place of a cognitive examination, candidates for recertification will be required to complete both the general thoracic and cardiac portions of the SESATS IV syllabus (Self-Education/Self-Assessment in Thoracic Surgery). It is not necessary for candidates to purchase

SESATS IV booklets prior to applying for recertification. SESATS IV booklets will be forwarded to candidates after their applications have been accepted.

Diplomates whose 10-year certificates will expire in 1995 may begin the recertification process in 1993. This new certificate will be dated 10 years from the time of expiration of the original certificate. Recertification is also open to any diplomate with an unlimited certificate and will in no way affect the validity of the original certificate.

The deadline for submission of applications is May 1, 1993. A recertification brochure outlining the rules and requirements for recertification in thoracic surgery is available upon request from the American Board of Thoracic Surgery, One Rotary Center, Suite 803, Evanston, IL 60201.

Comparison of Two Experimental Models for Assessment of Cardiac Preservation

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Previous studies from this institution using human cell cultures have suggested that University of Wisconsin solution is preferred for prolonged hypothermic storage for cardiac transplantation. The primary objective of this study was to evaluate the effectiveness of extended cardiac preservation with University of Wisconsin solution by assessing the time-related changes of purine metabolites using two different models of cold storage. Isolated rat hearts ($n = 6/\text{group}$) or human ventricular myocyte cultures ($n = 7$ dishes/group) were assessed after 0, 6, 12, and 24 hours in University of Wisconsin solution at 0°C using high-performance liquid chromatography. Adenosine triphosphate content decreased from 18.1 ± 5.4 to $9.6 \pm 2.7 \mu\text{mol/g}$ dried weight by 12 hours and to $1.0 \pm 0.6 \mu\text{mol/g}$ by 24 hours ($p < 0.0001$ by analysis of variance) in the rat model. Adenosine triphosphate content decreased from 0.64 ± 0.42 to 0.14 ± 0.11

$\text{nmol}/\mu\text{g}$ DNA at 6 hours and to $0.04 \pm 0.03 \text{ nmol}/\mu\text{g}$ DNA by 24 hours ($p < 0.00001$) in the cardiomyocytes. Inosine monophosphate content increased from 0.1 ± 0.2 to 10.8 ± 1.0 by 24 hours ($p < 0.0001$) in the rat studies. Inosine monophosphate values tended to increase up to 12 hours ($p = 0.06$) in the cell cultures and then declined. Adenosine concentration increased from 0.3 ± 0.3 to $2.3 \pm 0.9 \mu\text{mol/g}$ at 6 hours and declined thereafter ($p < 0.0005$) in the rodent hearts. Adenosine concentration increased from 0.03 ± 0.02 to $1.53 \pm 0.72 \text{ nmol}/\mu\text{g}$ DNA at 6 hours ($p < 0.0001$) in the cardiomyocytes. Human cell cultures may represent a more sensitive model to evaluate adenine nucleotides after cardiac storage conditions and avoid species-specific changes in purine degradation. Nucleoside contents are likely increased unphysiologically with this experimental technique.

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University of Wisconsin solution (UWS) at 0°C may be the preferred storage conditions for cardiac transplantation according to results from our laboratory [1–3] and others [4–10] and recent clinical trials [11, 12]. Previous studies from this institution investigated human cardiomyocytes as a screening model of organ preservation. Despite the potential advantages of using human cell cultures for evaluation of storage techniques [13], this methodology represents a substantial departure from the intact organ. Whole organ preservation with UWS at 0°C has been evaluated in these current studies, and the results compared with the findings obtained using human cardiomyocytes.

Material and Methods

Rat Protocol

Hearts were obtained from Sprague-Dawley rats (250 to 500 g). All animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" (NIH publication No. 85-23, revised 1985). Animals were anesthetized with an intraperitoneal injection of sodium pentobarbital. A median sternotomy was then performed, and the hearts were rapidly excised and

submerged in chilled normal saline solution. Control hearts were immediately immersed in liquid nitrogen after cardiac arrest (0 hours, $n = 6$). Experimental hearts were flushed with UWS, 15 mL/kg body weight, over a 2-minute interval. The hearts were subsequently stored at 0°C for 6, 12, or 24 hours ($n = 6/\text{group}$) in 15 to 20 mL of chilled UWS.

After the storage interval, the hearts were immersed in liquid nitrogen and then lyophilized. Tissue was homogenized on ice with 0.5 mol/L perchloric acid. Samples were centrifuged at 2,500 rpm for 10 minutes, and the supernatant was neutralized with 2 mol/L potassium hydroxide to a pH of 7.6 and reacidified with 0.1 mol/L perchloric acid to a pH of 6.8. Samples were frozen in liquid nitrogen, lyophilized, and stored at -80°C until reconstitution in 100 mmol/L $\text{NH}_4\text{H}_2\text{PO}_4$ buffer before analysis using high-performance liquid chromatography.

Cell Culture Protocol

Ventricular myocardium was obtained during elective repair of Tetralogy of Fallot from patients who had signed a consent form approved by the institutional human ethics committee. Human cardiomyocyte cultures were prepared as previously described with slight modifications [1–3]. Tissue was minced, after which the cells were dissipated with collagenase (0.1%) and trypsin (2%). The supernatant was collected. Cells were separated by centrifugation for 5 minutes at 2,000 rpm. The precipitated

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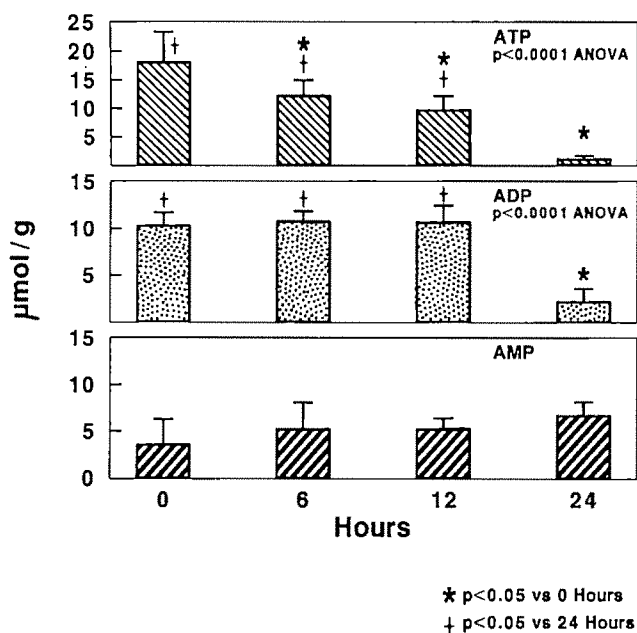


Fig 1. The results (mean $\pm$ standard deviation) of adenosine triphosphate (ATP), adenosine diphosphate (ADP), and adenosine monophosphate (AMP) levels in rodent hearts ($n = 6/\text{group}$) are displayed. Data are presented for control samples (0 hours) and after 6, 12, and 24 hours of hypothermic storage with University of Wisconsin solution. Probability values are presented for analysis of variance (ANOVA) where significant, and differences between means are specified with a multiple-comparison t test. The level of ATP had decreased by 6 hours and ADP after 24 hours, whereas no significant change occurred for AMP.

cells were suspended in culture medium containing 10% fetal bovine serum and Iscove's modified Dulbecco's medium (Gibco Laboratories Life Technologies Inc, Grand Island, NY) with 1% penicillin-streptomycin at 37°C with an environment of 5% CO_2 and an oxygen tension of 150 mm Hg.

Cells were grown until confluent, and then passage with trypsin performed. Fibroblasts and myocytes were manually separated and the identity of the myocytes verified using anti-actin [14] and anti-ventricular light chain 1 antibodies [15]. Experiments were performed using nonconfluent dishes ($n = 7/\text{group}$).

For the control studies (0 hours), the culture media was discarded and the cells were rinsed with chilled phosphate-buffered saline solution and then frozen with liquid nitrogen. For the experimental groups, the culture media was discarded and the cells were rinsed with phosphate-buffered saline solution. Ten milliliters of chilled UWS was then added to each dish. Cells were stored at 0°C for 1, 6, 12, or 24 hours.

After the preservation period, the storage fluid was discarded and the cells were rinsed with phosphate-buffered saline solution and then frozen with liquid nitrogen. The tissue was lyophilized and stored at -80°C. Nucleotides were extracted from myocytes based on a methodology described by Shryock and associates [16] as previously described.

The protocol for DNA quantification was based on the

method of Maniatis and colleagues [17]. The samples were assayed on a Beckman DU-40 spectrophotometer (Beckman Instruments Inc, Irvine, CA) at 260 nm.

Measurements

The levels of adenine nucleotides and their degradation products were measured using high-performance liquid chromatography according to a modification of the method of Hull-Ryde and associates [18] and employing the Waters Maxima 820 Chromatography Workstation computer program as previously described [3, 19]. Samples were maintained at 4°C and injected with an automatic injector (model 700 Satellite WISP; Waters Associates, Mississauga, ON, Canada). A step-gradient solvent delivery was accomplished via a Waters Solvent Select Valve and two reciprocating pumps (Waters Associates, models 501 and 510). The chromatographic column was a Radial-Pak Resolve C18 column with a 5- μm particle size (Waters Associates), which was operated in a radial compression module (Waters Associates, model RCM 8 $\times$ 10) at 175 kg/cm^2 . A programmable multiwave length detector (Waters Associates, model 490) was used to monitor the peaks. The previously mentioned equipment was controlled by a System Interface module (Waters Associates, model I-200). The system measured the levels of uric acid, adenosine triphosphate (ATP), inosine monophosphate, adenosine diphosphate (ADP), hypoxanthine, xanthine, adenosine monophosphate (AMP), inosine, adenosine, and 2'-O-methyladenosine (internal standard) at 254 nm. Peak areas were integrated by the Waters Maxima 820 computer program. The concentrations of the adenine nucleotides and their degradation products were expressed as micromoles per gram of freeze-dried weight for the rat studies and nanomoles per microgram of DNA for the cell culture studies.

Statistical Analysis

Data analysis was facilitated using Statistical Analysis System software (SAS Institute, Cary, NC) and a microcomputer. Data are summarized as the mean $\pm$ standard deviation in the text and figures. The treatment effect due to time within each group was tested initially using a one-way analysis of variance, and the differences between means were specified with Duncan's multiple range test [20]. A comparison of isolated organ and cell culture experiments was performed using percentage transformed data and two-way analysis of variance. Comparisons were performed initially with a percentage transformation of the data assuming the 0-hour mean values represent 100% and secondly expressing the data as a percentage of the mean 0 hour sum of all purine compounds. Statistical significance is assumed for p values less than 0.05.

Results

Part I

The results of the rat studies for ATP, ADP, and AMP are summarized in Figure 1. The level of ATP decreased from

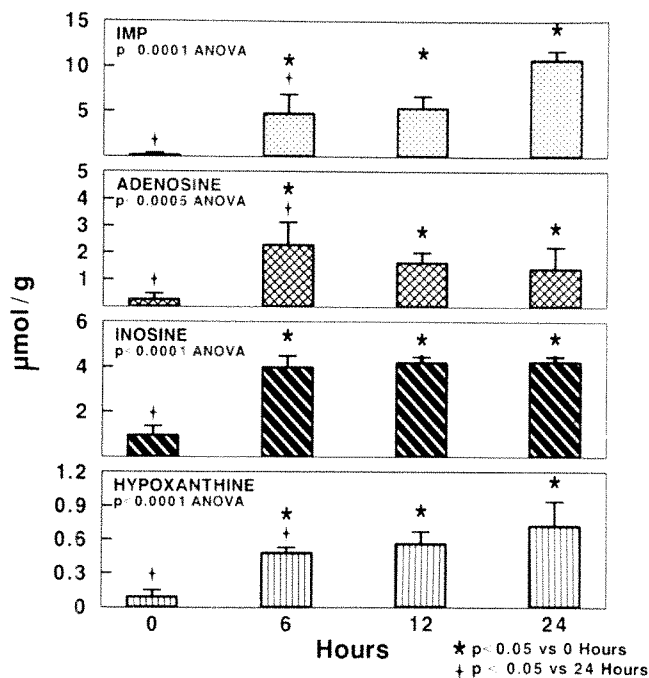


Fig 2. The results (mean $\pm$ standard deviation) of inosine monophosphate (IMP), adenosine, inosine, and hypoxanthine levels in rodent hearts ($n = 6/\text{group}$) are displayed. Data are presented for control samples (0 hours) and after 6, 12, and 24 hours of hypothermic storage with University of Wisconsin solution. Probability values are presented for analysis of variance (ANOVA) where significant, and differences between means are specified with a multiple-comparison t test. Inosine monophosphate was the most prominent degradation product identified following storage in the rodent heart.

18.1 $\pm$ 5.4 to 9.6 $\pm$ 12.7 $\mu\text{mol/g}$ by 12 hours. The level of ADP was maintained until 12 hours. Levels of ATP and ADP were severely depleted at 24 hours. The AMP concentration did not change significantly.

The serial changes of degradation products are depicted in Figure 2. Inosine monophosphate concentration increased from 0.1 $\pm$ 0.2 to 10.7 $\pm$ 1.0 $\mu\text{mol/g}$ at 24 hours. Adenosine level increased from 0.3 $\pm$ 0.3 to 2.3 $\pm$ 0.9 $\mu\text{mol/g}$ by 6 hours but decreased progressively subsequently. Both inosine and hypoxanthine concentrations increased progressively (inosine: 0 hour = 0.9 $\pm$ 0.5, 24 hour = 4.2 $\pm$ 0.3 $\mu\text{mol/g}$; hypoxanthine: 0 hour = 0.1 $\pm$ 0.1, 24 hours = 0.7 $\pm$ 0.2 $\mu\text{mol/g}$; $p < 0.0001$). The levels of xanthine and uric acid were always small (Table 1).

The proportional contribution of each of the purine metabolites is depicted in Figure 3. The total concentra-

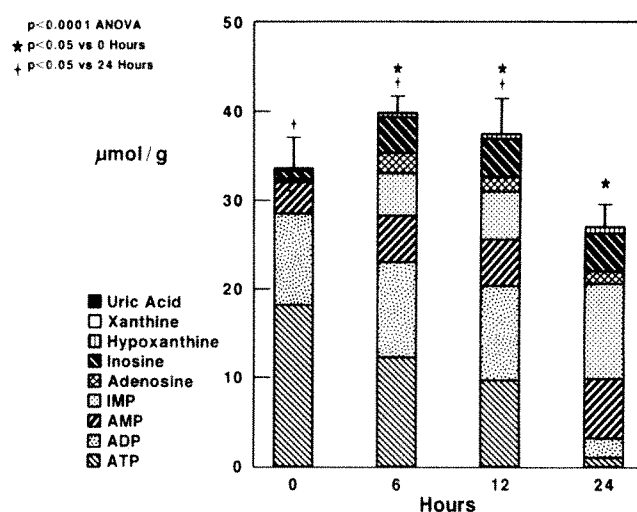


Fig 3. The proportional contributions of each of the purine metabolites are presented for the rat heart studies ($n = 6/\text{group}$). Probability values are given for analysis of variance (ANOVA), and differences between means are specified with a multiple-comparison t test. Total measured purine compounds had increased at 6 and 12 hours but had decreased by 24 hours. (ADP = adenosine diphosphate; AMP = adenosine monophosphate; ATP = adenosine triphosphate; IMP = inosine monophosphate.)

tion increased from 33.4 $\pm$ 3.6 to 39.6 $\pm$ 1.9 $\mu\text{mol/g}$ by 6 hours but had decreased to 27.0 $\pm$ 2.6 $\mu\text{mol/g}$ by 24 hours.

Part II

The results of ATP, ADP, and AMP levels for the cell culture experiments are summarized in Figure 4. The level of ATP decreased from 0.64 $\pm$ 0.42 to 0.14 $\pm$ 0.11 nmol/ μg DNA by 6 hours and to 0.04 $\pm$ 0.03 nmol/ μg DNA by 24 hours. The levels of ADP and AMP both declined similarly.

The serial changes in degradation products are displayed in Figure 5. Inosine monophosphate values increased by 12 hours but declined subsequently ($p = 0.06$). Adenosine concentration increased from 0.03 $\pm$ 0.02 to 1.53 $\pm$ 0.72 nmol/ μg DNA at 6 hours, inosine concentration increased from 0.04 $\pm$ 0.04 to 0.74 $\pm$ 0.42 nmol/ μg DNA at 6 hours, and hypoxanthine concentration increased from 0.01 $\pm$ 0.01 to 0.13 $\pm$ 0.07 nmol/ μg DNA at 6 hours. Adenosine, inosine, and hypoxanthine levels each remained increased. The values of xanthine and uric acid were generally unmeasurable in the cell culture studies.

Table 1. Xanthine and Uric Acid in Rat Hearts ($n = 6$ hearts/group)

Variable	Time (hours)				p Value (ANOVA)
	0	6	12	24	
Xanthine ($\mu\text{mol/g}$ dried wt)	0.07 $\pm$ 0.06	0.04 $\pm$ 0.03	0.02 $\pm$ 0.02 ^a	0.04 $\pm$ 0.06	NS
Uric acid ($\mu\text{mol/g}$ dried wt)	0.10 $\pm$ 0.03 ^b	0 ^a	0 ^a	0 ^a	0.0001

^a $p < 0.05$ versus 0 hours. ^b $p < 0.05$ versus 24 hours.

ANOVA = analysis of variance; NS = not significant.

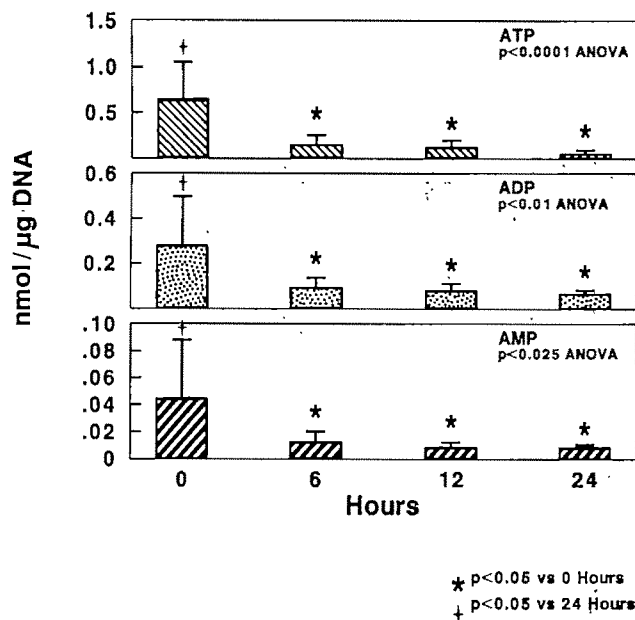


Fig 4. The results (mean $\pm$ standard deviation) of adenosine triphosphate (ATP), adenosine diphosphate (ADP), and adenosine monophosphate (AMP) levels in human cell cultures ($n = 7$ dishes/group) are displayed. Data are presented for control samples (0 hours) and after 6, 12, and 24 hours of hypothermic storage with University of Wisconsin solution. Probability values are presented for analysis of variance (ANOVA) where significant, and differences between means are specified with a multiple-comparison t test. The level of each of the nucleotides had declined significantly by 6 hours in the human cell experiments.

The proportional contribution of each of the purine metabolites is depicted in Figure 6. The total value increased from 1.0 ± 0.7 to a maximum of 3.3 ± 0.6 nmol/ μ g DNA at 12 hours, largely secondary to adenosine and inosine.

Part III

A quantitative comparison of the rat and human storage data is presented in Tables 2 and 3. The data are reported as percentages of the mean 0-hour values in Table 2. The data are reported as percentages of the mean 0-hour total purine values in Table 3 (ie, relative to $33.4 \mu\text{mol/g}$ for rat results and $1.0 \text{ nmol}/\mu\text{g}$ for human results). The p values associated with the F test for either the main effect (rat versus human) or interaction [time $\times$ (rat versus human)] are presented. Levels of ATP, ADP, and AMP are severely depleted more rapidly in the human than in the rat experiments. Inosine monophosphate is a more important degradation product in the rat studies than in the human. Adenosine, inosine, and hypoxanthine levels increase to a greater extent in the human compared with the rat preservations. Xanthine and uric acid values are small in both studies, but tended to be higher in the rat experiments.

Comment

Previous studies from this institution have assessed prolonged hypothermic storage using human cell cultures as

a screening model [1-3]. These studies indicated that UWS was preferred to Stanford cardioplegia, modified Euro-Collins, or phosphate-buffered saline solution. Other findings were that endothelial cells were, in general, more tolerant to cold storage than ventricular myocytes and that preservation was enhanced with progressive temperature reduction [2]. We selected the 6-hour storage time to represent the current upper limit of tolerable ischemic time for cardiac transplantation, although experimental preparations have variable success after 12 to 24 hours [21, 22].

Isolated cell cultures provide an excellent model for metabolic investigations of myocardial tissue [13]. Human tissue is employed for these studies, eliminating concerns relative to species differences. Different tissues can be analyzed separately, for example, endothelial cell and cardiomyocytes. Despite the potential advantages of using cell cultures, this method represents a substantial departure from the intact organ. We therefore wished to compare results obtained using this technique with similar protocols and end points using an intact organ. Statistical comparisons were conducted with percentage transformed data to eliminate the differences in units for the rat heart and human cell experiments. A two-way analysis of variance was performed and results reported for the main

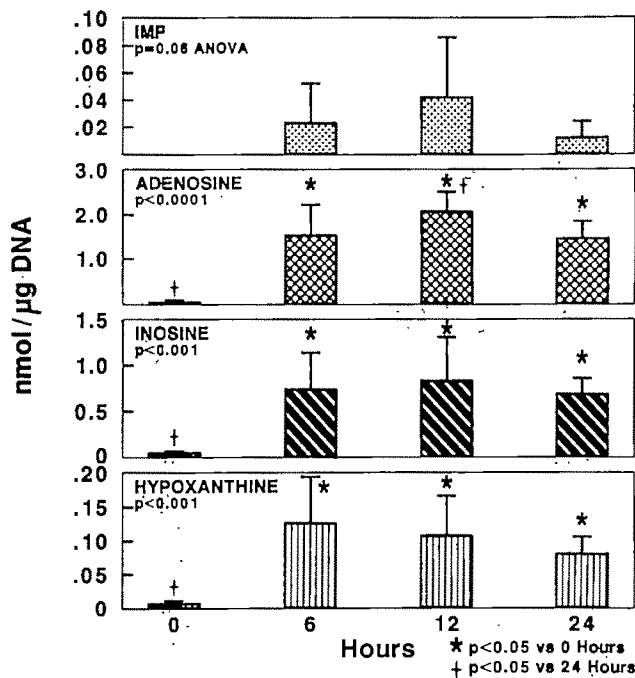


Fig 5. The results (mean $\pm$ standard deviation) of inosine monophosphate (IMP), adenosine, inosine, and hypoxanthine levels in human cell cultures ($n = 7$ dishes/group) are displayed. Data are presented for control samples (0 hours) and after 6, 12, and 24 hours of hypothermic storage with University of Wisconsin solution. Probability values are presented for analysis of variance (ANOVA) where significant, and differences between means are specified with a multiple-comparison t test. Pronounced elevations of adenosine and inosine levels were identified. This likely reflects diffusion of adenosine contained in University of Wisconsin solution into the myocyte and subsequent deamination.

effect (rat versus human) or interaction [time $\times$ (rat versus human)].

Qualitatively, the results of the two models are similar in many respects. Levels of adenine nucleotides decline, whereas levels of inosine monophosphate, adenosine, inosine, and hypoxanthine increase and those of xanthine and uric acid tend to decrease. Quantitatively, severe differences do exist between these two models in terms of the magnitude or rate of change from initial values or in terms of the proportional contribution relative to the total purine content. Some of these differences could be secondary to the differences in whole heart versus isolated cell, whereas others may be species-dependent.

Adenosine triphosphate concentration decreased to less than 25% of control values in the cell culture studies by 6 hours in association with significant depression of ADP and AMP values. This contrasted with a milder depression of the rodent ATP values, maintenance of ADP values, and increase in AMP values. Whole heart ATP levels after medium-term storage are generally well preserved in other experimental protocols [4, 8, 10] with UWS, consistent with the data from our studies. Human cell cultures appear to be a more sensitive model to assess interventions involving adenine nucleotides.

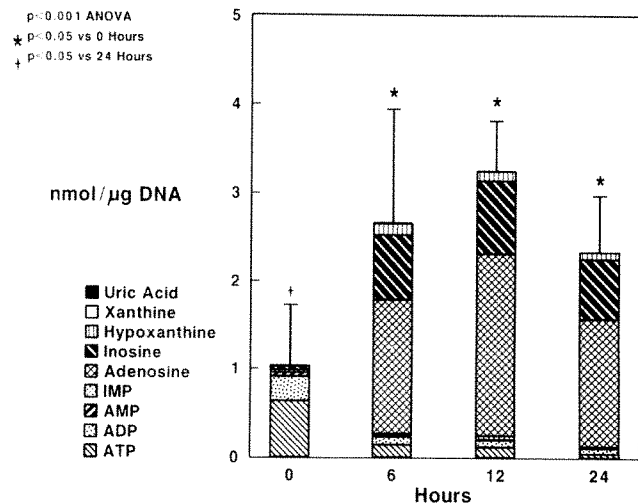


Fig 6. The proportional contributions of each of the purine metabolites are presented for the cell culture studies ($n = 7$ dishes/group). Probability values are given for analysis of variance (ANOVA), and differences between means are specified with a multiple-comparison t test. The sum of metabolites had increased by 6 hours, largely due to the contributions of adenosine and inosine. (ADP = adenosine diphosphate; AMP = adenosine monophosphate; ATP = adenosine triphosphate; IMP = inosine monophosphate.)

Table 2. Rat Versus Human Comparison (percentage transformation: mean prestorage values = 100%)^a

Variable	Hours				<i>p</i> Value ^b (analysis of variance)	
	0	6	12	24	Main Effect	Interaction
ATP						
Rat	100 ± 30	68 ± 17	53 ± 15	5 ± 3	0.0160	0.0942
Human	100 ± 65	22 ± 17 ^c	18 ± 15 ^c	7 ± 5		
ADP						
Rat	100 ± 13	104 ± 10	104 ± 16	21 ± 13	0.0003	0.0027
Human	100 ± 81	33 ± 18 ^c	28 ± 20 ^c	23 ± 8		
AMP						
Rat	100 ± 74	147 ± 79	147 ± 31	188 ± 40	0.0001	0.0026
Human	100 ± 103	28 ± 22 ^c	18 ± 11 ^c	18 ± 5 ^b		
Adenosine						
Rat	100 ± 108	910 ± 354	652 ± 176	564 ± 340	0.0001	0.0001
Human	100 ± 60	5,167 ± 2,428 ^c	7,006 ± 1,570 ^c	4,899 ± 1,430 ^c		
Inosine						
Rat	100 ± 50	423 ± 60	446 ± 33	450 ± 30	0.0001	0.0072
Human	100 ± 91	1,886 ± 1,064 ^c	2,124 ± 1,259 ^c	1,753 ± 479 ^c		
Hypoxanthine						
Rat	100 ± 74	533 ± 67	626 ± 129	798 ± 259	0.0001	0.0104
Human	100 ± 94	2,111 ± 1,165 ^c	1,795 ± 1,021 ^c	1,350 ± 459		
Xanthine						
Rat	100 ± 83	62 ± 49	31 ± 26	57 ± 79	0.0825	>0.10
Human	100 ± 140	0	17 ± 45	0		
Uric acid						
Rat	100 ± 29	0	0	0	>0.10	>0.10
Human	100 ± 180	0	0	0		

^a Inosine monophosphate results not presented as initial values were unmeasurable in the human studies, precluding percentage transformation. ^b Main effect refers to the (rat versus human) effect. Interaction refers to the [time $\times$ (rat versus human)] effect. ^c $p < 0.05$ versus rat value.

ADP = adenosine diphosphate; AMP = adenosine monophosphate; ATP = adenosine triphosphate.

Table 3. Rat Versus Human Comparison (percentage transformation: total prestorage purine values = 100%)

Variable	Hours				p Value (analysis of variance)*	
	0	6	12	24	Main Effect	Interaction
ATP						
Rat	54 ± 16	37 ± 9	29 ± 8	3 ± 2	0.0951	0.0302
Human	61 ± 40	13 ± 11 ^b	11 ± 9 ^b	4 ± 3		
ADP						
Rat	31 ± 4	32 ± 3	32 ± 5	6 ± 4	0.0001	0.0010
Human	27 ± 22	9 ± 5 ^b	8 ± 6 ^b	6 ± 2		
AMP						
Rat	11 ± 8	16 ± 8	16 ± 3	20 ± 4	0.0001	0.0083
Human	4 ± 4	1 ± 1 ^b	1 ± 1 ^b	1 ± 1 ^b		
IMP						
Rat	0.3 ± 0.6	14 ± 6	16 ± 4	32 ± 3	0.0001	0.0001
Human	0.1 ± 0.1	2 ± 3 ^b	4 ± 4 ^b	1 ± 1 ^b		
Adenosine						
Rat	0.7 ± 0.8	7 ± 3	5 ± 1	4 ± 3	0.0001	0.0041
Human	3 ± 2 ^b	147 ± 70 ^b	200 ± 45 ^b	140 ± 41 ^b		
Inosine						
Rat	3 ± 1	12 ± 2	13 ± 1	13 ± 1	0.0001	0.0025
Human	4 ± 3	71 ± 40 ^b	80 ± 47 ^b	66 ± 18 ^b		
Hypoxanthine						
Rat	0.3 ± 0.2	1 ± 0.2	2 ± 0.3	2 ± 1	0.0001	0.0025
Human	0.6 ± 0.5	13 ± 7 ^b	10 ± 6 ^b	8 ± 3 ^b		
Xanthine						
Rat	0.2 ± 0.2	0.01 ± 0.1	0.1 ± 0.1	0.1 ± 0.2	>0.10	>0.10
Human	0.4 ± 0.5	0 ^b	0.1 ± 0.2	0		
Uric acid						
Rat	0.3 ± 0.1	0	0	0	0.0001	0.0001
Human	0.1 ± 0.1 ^b	0	0	0		

* Main effect refers to the (rat versus human) effect. Interaction refers to the [time × (rat versus human)] effect. ^b p < 0.05 versus rat value.

Inosine monophosphate levels increased to a much greater extent in the present rodent experiments than in the cell culture studies. Previous biopsy studies performed in coronary bypass patients undergoing elective revascularization procedures similarly identified only small quantities of inosine monophosphate in human myocardium [19]. This suggests that AMP is largely metabolized through adenosine in human myocardium whereas AMP-inosine monophosphate conversion is a more important pathway in the rat heart. Studies assessing the cardioprotective effects of adenosine supplementation [23-25] or blockers of adenosine metabolism [26, 27] may not be adequately evaluated using a species less dependent on AMP-adenosine conversion.

We have previously reported that human tissue levels of xanthine and uric acid were very small in isolated cardiomyocyte cultures [3] or left ventricular biopsy specimens after cardioplegic arrest [19]. Other investigators suggest that xanthine oxidase activity is minimal in human myocardium, although this remains controversial. It is probable that the differences in inosine monophosphate, xanthine, and uric acid levels are species-dependent.

The level of adenosine (and inosine after deamination)

increased to a greater extent in the human compared with rodent experiments. The concentration of total purine compounds increased threefold in the cell culture studies, largely secondary to the increase of adenosine and inosine (see Fig 6). Adenosine is present in UWS in a concentration of 5 mmol/L. As the isolated cardiomyocytes are submerged in a relatively large volume of storage solution during preservation, it is anticipated that diffusion of the permeable adenosine would be greater in the cell culture experiments, compared with the isolated rat heart, where diffusion is limited. The level of adenosine increased to 8.62 ± 1.18 nmol/mg protein in studies performed by Yeh and associates [5] using isolated rodent hearts. It is probable that the differences in adenosine and inosine concentrations represent model effects.

We have conducted long-term cardiac storage experiments with UWS using isolated rat heart and human cultured cardiomyocytes. Preservation for 24 hours is unsatisfactory, whereas limited protection is provided for 6 to 12 hours. Adenine nucleotides are depleted more rapidly in the cell culture studies. Inosine monophosphate (and, to a lesser degree, xanthine and uric acid) accumulates to a greater degree in the rat heart experiments, which likely represents a species-specific finding.

Adenosine and inosine levels increase more in the isolated cells, which probably is model-dependent.

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Distal Aortic Arch Aneurysmectomy and Coronary Revascularization Through a Left Thoracotomy

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A successful single operation of a distal aortic arch aneurysm and coronary artery disease through a left lateral thoracotomy using a simple hypothermic retrograde cerebral perfusion technique for cerebral protection in a 64-year-old man is reported. During ventricular fibrillation accompanying cooling to 15°C, a left internal

thoracic artery was anastomosed with the left anterior descending coronary artery, and the aneurysm was replaced with a patch during hypothermic retrograde cerebral perfusion.

(*Ann Thorac Surg* 1993;55:151-2)

Aortic aneurysm is often associated with coronary artery disease. Replacement of the ascending aorta and the aortic arch with coronary artery bypass grafting through a median sternotomy has been reported [1]; here we report replacement of the distal aortic arch with coronary artery bypass grafting through a left lateral thoracotomy.

We have recently reported that hypothermic cerebral retrograde perfusion can be achieved by simply elevating the central venous pressure in Trendelenburg position when the aortic arch is open [2]. During profound hypothermic perfusion of the lower half of the body with the descending aorta occluded, venous blood rich in oxygen supplied this oxygen to the brain, protecting it over a long period of cerebral circulatory arrest. Because this technique simplifies the operation, eliminating dissection of the arch vessels and the other special preparatory procedures, it can be used not only for a median approach but also for a lateral thoracotomy approach, which is suitable for operation on a distal aortic arch aneurysm.

We have performed distal aortic arch aneurysmectomy by this simple hypothermic method immediately after carrying out coronary artery bypass grafting using the left internal thoracic artery during the cooling process.

A 64-year-old man with a saccular type of distal aortic arch aneurysm had three-vessel coronary heart disease (No. 1, 100%; No. 6, 75%; No. 11, 99%) without angina or serious changes in the electrocardiogram. He had been suffering from systemic arteriosclerotic diseases such as old cerebral infarction with right hemiparesis, abdominal aortic aneurysm, and arteriosclerosis obliterans with occlusion of the right iliac artery.

Operation was performed through a left lateral thoracotomy (Fig 1). The left internal thoracic artery was dissected. The left femoral vein was cannulated to provide drainage of the right atrium, and the descending aorta was cannulated because of the difficulty of perfusion through the femoral artery. The left ventricle was vented through the apex. Cooling was initiated using regular cardiopulmonary bypass. During the ventricular fibrillation that accompanied cooling to 15°C, a left internal thoracic artery graft was anastomosed with the left anterior descending coronary artery. We also attempted to anastomose a saphenous vein graft to the posterior descending branch of the right coronary artery, but this graft was abandoned because dissection had occurred in this branch. The small left circumflex artery and the good collateral flow from the left anterior coronary artery to the right coronary artery offered assurance for the success of single bypass grafting.

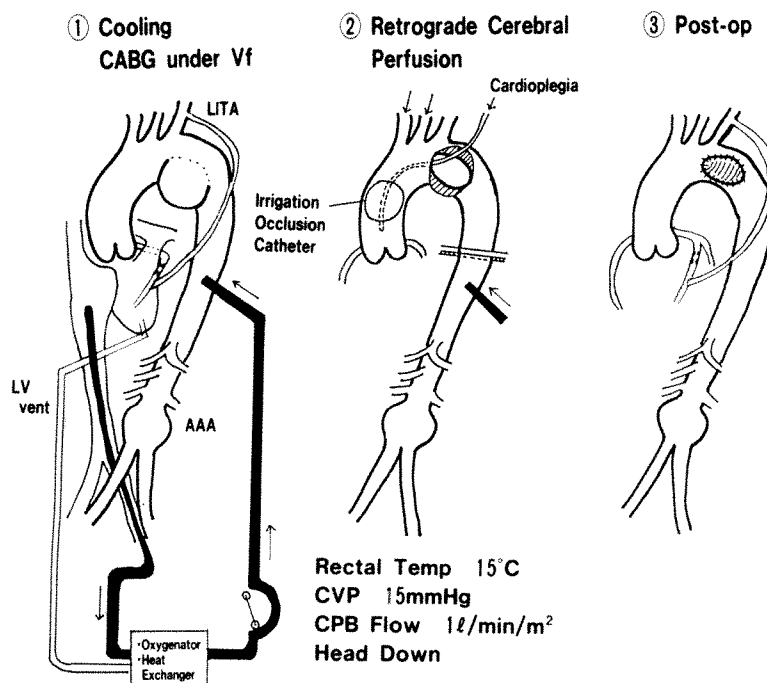
After the rectal temperature reached 15°C, the descending aorta was clamped proximal to the cannulation site and cardiopulmonary bypass flow was reduced to 1,500 mL/min, 1 L/min/m². The patient was then placed in a mild Trendelenburg position, and the central venous pressure was raised to 15 mm Hg, slightly occluding the venous line of the pump. An incision was made in the aortic arch without clamping the arch vessels, and an aortic irrigation occlusion catheter was introduced into the ascending aorta through this incision for crystalloid cardioplegia and for blocking the blood flow from the left ventricle.

During retrograde cerebral perfusion carried out to supply oxygen to the brain, the saccular aortic arch aneurysm was replaced by a patch. After the descending aorta was declamped, the cardiopulmonary bypass flow was raised to the normal flow rate, and rewarming was initiated. In this period, cerebral and coronary reperfusion was commenced. The remainder of the operation was completed in the usual manner. Operation time was 587

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Fig 1. Diagram of the operative procedure of a single operation for distal aortic arch aneurysmectomy with coronary artery bypass grafting through a left lateral thoracotomy. (AAA = abdominal aortic aneurysm; CABG = coronary artery bypass grafting; CPB = cardiopulmonary bypass; CVP = central venous pressure; LITA = left internal thoracic artery; LV = left ventricular; Vf = ventricular fibrillation.)



minutes, cardiopulmonary bypass time 238 minutes, cardiac and cerebral arrest time 70 minutes.

During hypothermic retrograde cerebral perfusion, substantial extraction of oxygen and lactate was noted in the brain. In the venous blood entering the cardiopulmonary bypass, the oxygen tension was 89 mm Hg, oxygen saturation was 96.4%, and the lactate level was 4.1 mmol/L (37.3 mg/dL). The retrograde perfusion blood in the carotid artery had an oxygen tension of 45 mm Hg, oxygen saturation of 71.4%, and a lactate level of 3.8 mmol/L (34.0 mg/dL). These data indicated substantial amounts of oxygen and lactate were extracted by the brain even in profound hypothermia.

The postoperative course of this patient was uneventful. There were no signs of neurologic or myocardial damages. Postoperative coronary angiogram revealed the patent graft. Abdominal aortic aneurysmectomy with a Y-shaped graft was successfully performed 6 months later through a retroperitoneal approach.

Comment

Retrograde cerebral perfusion performed under profound hypothermia by elevation of the central venous pressure is very simple, and requires neither special handling or dissection of the arch vessels, vena cava, and the ascending aorta nor any special bypass circuits. It can be used for a lateral thoracotomy using femoral vein drainage and aortic root perfusion by means of an irrigation occlusion catheter introduced through an incision at the site of an aneurysm.

Coronary artery bypass grafting through a lateral thoracotomy has been reported mainly for coronary reoperations [3-5]. Coronary artery disease associated with a

distal aortic arch aneurysm or a descending aortic aneurysm has generally been treated by earlier coronary artery bypass grafting or percutaneous transluminal coronary angioplasty [1]. The present one-stage operation had the advantages of reducing the physical and economic costs of two separate cardiopulmonary bypass operations, and of providing more adequate myocardial revascularization than balloon angioplasty. With this technique coronary artery bypass grafting can be carried out during cooling to deep hypothermia without substantial extension of the operation time, the internal thoracic artery is more easily dissected than through a median sternotomy, and the descending aorta can, if necessary, be selected as the cannulation site for cardiopulmonary bypass.

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Extracorporeal Membrane Oxygenation for Severe Heart Failure After Fontan Operation

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A 10-year-old boy with tricuspid atresia and Glenn anastomosis underwent a modified Fontan operation. After the operation, the pressure in the inferior vena cava increased, leading to oliguria and ascites. After the creation of continuity between the superior vena cava and the inferior vena cava to reduce the pressure gradi-

ent, there remained an elevated right atrial pressure. Six days of extracorporeal membrane oxygenation effectively stabilized his hemodynamics and organ function and allowed an excellent outcome.

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The Fontan-type operation was developed to treat tricuspid atresia [1, 2]. Operative mortality and long-term survival are acceptable [3], but persistently elevated right atrial pressure (RAP) postoperatively sometimes causes renal failure, ascites, or hepatic failure. This condition is refractory to medical management, and extracorporeal membrane oxygenation (ECMO) is the most effective treatment presently available. We report a patient with tricuspid atresia successfully treated with ECMO for elevated RAP after a modified Fontan operation.

A 10-year-old boy with tricuspid atresia was admitted to our hospital for a corrective operation. He had visceral and atrial situs solitus, and the ventriculoarterial connections were normal. A large atrial septal defect, a muscular ventricular septal defect, a rudimentary right ventricle, and pulmonary valve stenosis were present. He had undergone a left Blalock-Taussig shunt and Glenn anastomosis previously. His weight was 31.8 kg, his height was 142 cm, and generalized cyanosis was noted on admission. Hematologic examination showed polycythemia (hematocrit, 0.59), and electrocardiography indicated left-axis deviation and left ventricular hypertrophy. Angiography revealed a widely patent Glenn anastomosis and an occluded left Blalock-Taussig shunt (Fig 1).

We performed a modified Fontan operation using a technique based on the method of Björk and associates [2]. Cardiopulmonary bypass was instituted, and a U-shaped incision was made in the right atrial appendage. The atrial septal defect was closed with an equine pericardial patch, and the main pulmonary artery (PA) was incised longitudinally to the anterior wall of the hypoplastic right ventricle. The ventricular septal defect was closed by direct suture, and the "floor" of the conduit, which had been created by the right atrial appendage, was

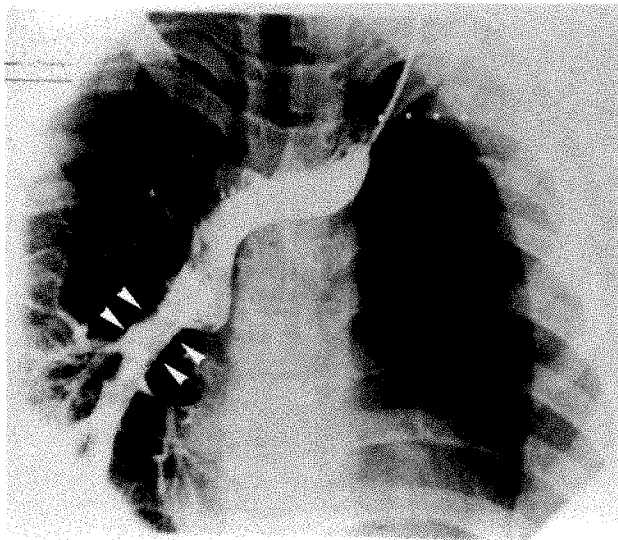
sutured to the everted right edge of the ventriculotomy. The anterior aspect of the atrioventricular communication was covered by an equine pericardial "roof," which was extended onto the main PA. At this point, blood flow from the superior vena cava drained into the right PA through the Glenn shunt, and flow from the inferior vena cava (IVC) drained into the left PA through the right atrium and right ventricle.

The postoperative course was uneventful until postoperative day 4, when oliguria and ascites developed. The IVC pressure was 23 mm Hg, which was 8 mm Hg greater than in the superior vena cava. Diuretics and catecholamines were ineffective, and we decided to reduce the IVC pressure surgically to improve perfusion of the abdominal organs. We created an anastomosis between the right atrium and the left brachiocephalic vein using a ringed expanded polytetrafluoroethylene graft (Gore-Tex; W.L. Gore & Assoc, Flagstaff, AZ; 12 mm in diameter). The pressure in the IVC, right atrium, and superior vena cava was 20 mm Hg after the anastomosis was opened.

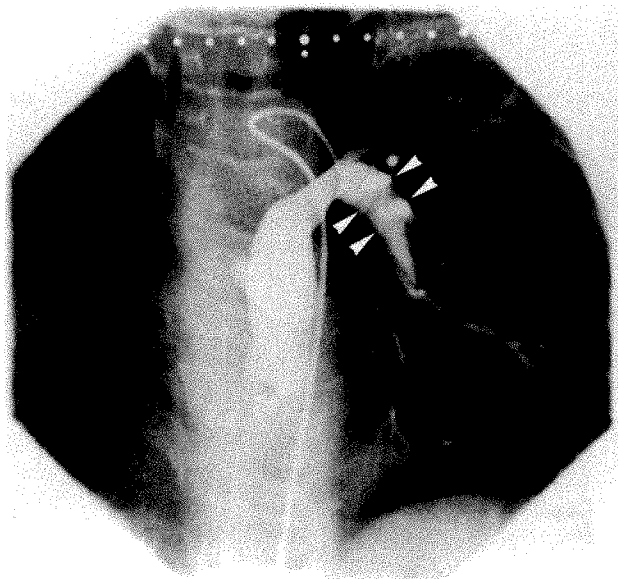
The next morning, the RAP exceeded 25 mm Hg, and low cardiac output syndrome developed (Fig 2). Renal and liver function deteriorated, and we believed that multiorgan failure was inevitable without heroic intervention. We decided to initiate ECMO to reduce IVC pressure and increase cardiac output. The circuit was constructed using a 24F venous cannula, a roller pump, a silicone hollow fiber oxygenator (Merasilox; Senko Medical Instrument, Tokyo, Japan), and a 12F arterial cannula. The venous cannula was placed in the right femoral vein, and the arterial cannula was placed in the right femoral artery through an artificial graft (Gore-Tex). Extracorporeal membrane oxygenation was started at a flow rate of 1.5 L/min. Hemodynamics stabilized immediately, and the RAP decreased to less than 18 mm Hg. Heparin and nafamostat mesilate (a protease inhibitor) were administered to prevent coagulation, and the activated coagulation time was maintained at approximately 200 seconds. The extracorporeal continuous ultrafiltration method was

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A



B

Fig 1. Preoperative pulmonary arteriography in a 10-year-old boy with tricuspid atresia. (A) Right pulmonary arteriography through the left brachiocephalic vein to Glenn shunt. (B) Left pulmonary arteriography through the inferior vena cava. Arrows indicate the right and left pulmonary arteries.

used to remove fluid simultaneously because oliguria persisted. The membrane oxygenator was replaced 3 days after the initiation of ECMO. The flow rate of ECMO was reduced gradually after 4 days, and the patient was weaned off of ECMO on the sixth day. Hemodialysis was continued for 1 month because of persistent renal failure. Renal function eventually recovered, and the urine output exceeded 1,500 mL/day, with serum urea nitrogen and creatinine concentrations within normal limits. Before ECMO, the glutamic-pyruvic transaminase concentration was 3,678 IU/mL, and it began to decrease soon thereafter. The RAP stabilized at 15 mm Hg 20 days after the operation.

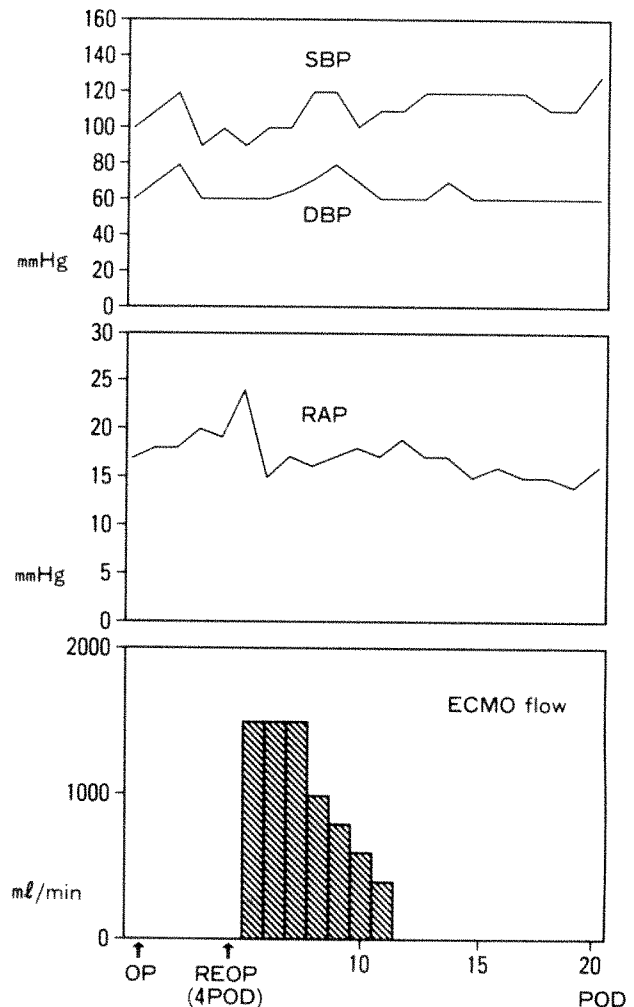


Fig 2. Blood pressure, right atrial pressure, and assisting flow rate after the Fontan procedure. (DBP = diastolic blood pressure; ECMO = extracorporeal membrane oxygenation; POD = postoperative day; RAP = right atrial pressure; REOP = reoperation [the addition of a shunt between the right atrium and left brachiocephalic vein]; SBP = systolic blood pressure.)

Right atrigraphy was performed 3 months after operation and showed that contrast medium from the right atrium drained into the right PA through the graft between the right atrium and left brachiocephalic vein and into the left PA without delay (Fig 3). Respiratory insufficiency due to transient postoperative phrenic nerve palsy necessitated mechanical ventilation for 2 months. The patient subsequently did well and was discharged from the hospital 4 months after the operation. He now lives a normal life with only a restriction on strenuous physical activity.

Comment

The modified Fontan operation has been established as a physiologic correction for tricuspid atresia. However, elevated RAP postoperatively has been a major problem and can lead to renal failure, ascites, and other organ

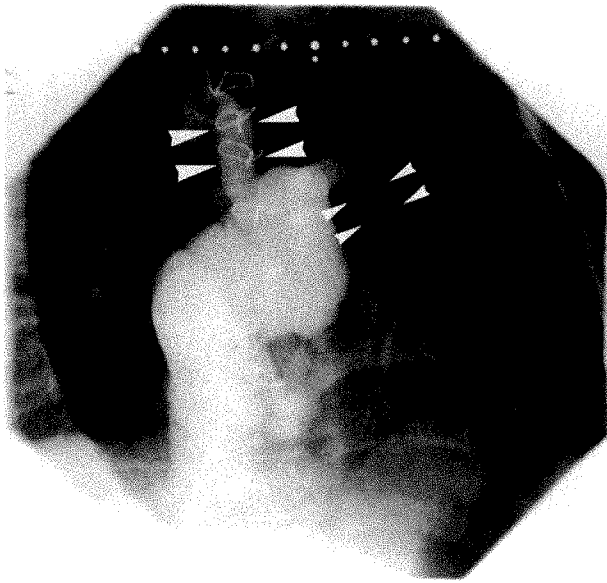


Fig 3. Right atriography 3 months after the Fontan procedure: large arrows indicate the graft between the right atrium and left brachiocephalic vein, and small arrows indicate the left pulmonary artery.

failure. Kirklin and associates [4] have recommended that a takedown of the Fontan repair should be considered when the immediate postoperative RAP reaches 22 mm Hg. In our patient, the Fontan operation combined with the previous Glenn shunt produced a pressure gradient between the superior vena cava and the IVC, which caused hypertension in the IVC. Although DeLeon and colleagues [5] have noted that the Glenn shunt plays a major role in minimizing postoperative hemodynamic instability, retrospectively, we believed the capacity of the left pulmonary vascular bed was inadequate in this case

and that the Glenn shunt was responsible for the pressure gradient between the superior vena cava and the IVC. The morning after reoperation, the RAP remained markedly elevated (25 mm Hg) despite of the elimination of the pressure gradient. We elected not to take down the Fontan repair but to employ ECMO in the hope that the capacity of the pulmonary vascular bed would increase rapidly. In fact, the patient was weaned from ECMO within 6 days. Extracorporeal membrane oxygenation is one of the most powerful techniques of circulatory support after repair of congenital heart disease [6]. As in this case, it can stabilize the circulatory state with a decrement in the RAP.

Although it is needless to say that anatomic problems, if present, must be resolved in the first place, ECMO, as an alternative to takedown, should be considered when low cardiac output and oliguria secondary to high RAP occur after Fontan repair.

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Thoracoscopic Drainage and Resection of Giant Mediastinal Cyst

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Video thoracoscopy is being used with increasing frequency by thoracic surgeons. Although initially used primarily for simple diagnostic purposes, improved instrumentation and evolving expertise have allowed for the performance of increasingly complex therapeutic procedures. We present a case of a giant subcarinal bronchogenic cyst in an elderly man with multiple med-

ical problems. The cyst nearly occluded the bronchus intermedius and resulted in recurrent respiratory tract infections. Using video thoracoscopy, the cyst was drained and the wall of the cyst was resected successfully with minimal concomitant morbidity.

(Ann Thorac Surg 1993;55:156-8)

A 68-year-old former steel worker came to the St. Louis University Hospital with a complaint of recurrent respiratory tract infections. During the previous 2 years these infections had occurred more frequently and persisted for 2 to 3 weeks despite oral antibiotics. The infections were characterized by intermittent fevers and chills, a productive cough, and right midthoracic posterior chest pain. A chest roentgenogram showed a 10-cm mediastinal mass (Fig 1A). The presence of this mass was confirmed on a computed tomographic scan, which showed a large cystic lesion in the mediastinum that laterally displaced and compressed the bronchus intermedius (Fig 1B). The computed tomographic findings were read as consistent with a bronchogenic cyst. Bronchoscopy confirmed extrinsic compression on the posterior membranous wall of the trachea, which produced near-occlusion at the bronchus intermedius. An attempt at transbronchial drainage via bronchoscopy was made. No fluid could be drawn through a 19-gauge needle advanced through the widened carina into the area of the cystic mass. Attempts at computed tomography-guided percutaneous drainage also proved unsuccessful. The patient was referred to St. Louis University Hospital for consideration of surgical resection of the cyst to prevent recurrent respiratory tract infections.

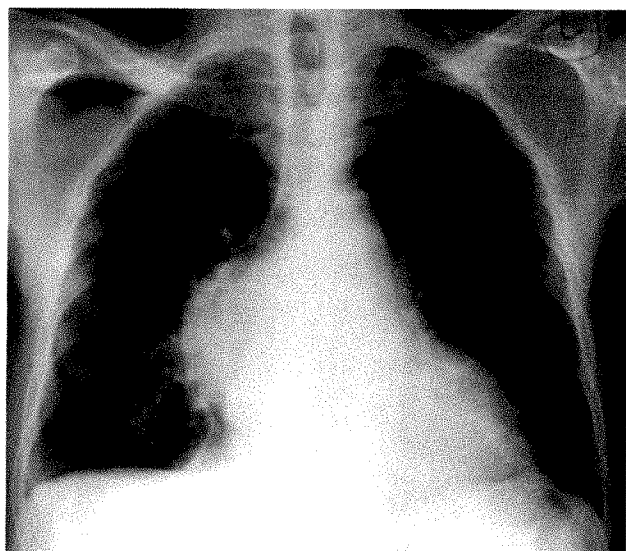
The patient had a 60-pack-year smoking history, and pulmonary function tests revealed moderately severe chronic obstructive pulmonary disease with a forced vital capacity of 2.22 L (60% of predicted) and a forced expiratory volume in 1 second of 1.42 L (56% of predicted). In addition, the patient's medical history included two anterior myocardial infarctions in 1985 and 1986 requiring percutaneous transluminal coronary angioplasty for postinfarction angina after each. A third infarction occurred in 1990, and since that time the patient has

continued to have intermittent angina episodes. A recent cardiac catheterization revealed occlusion of the left anterior descending and right coronary arteries with severe anterior apical and inferior hypokinesis. The left ventricular ejection fraction was 0.23 with a left ventricular end-diastolic pressure of 40 mm Hg. The cardiac index was $2.01 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$, and marked pulmonary hypertension was found with a pulmonary artery pressure of 70/35 mm Hg and a peripheral vascular resistance of $402 \text{ dynes} \cdot \text{s/cm}^5$.

The patient was thought to have a major operative risk for thoracotomy and cyst excision. A decision was made to proceed with attempted cyst drainage and resection using video thoracoscopy. At the time of operation, a pulmonary artery thermodilution catheter and arterial line were inserted. The patient underwent intubation with a double-lumen endotracheal tube, was placed in the left lateral decubitus position, and was prepared and draped in standard fashion as if for a right thoracotomy. One-centimeter skin incisions were made in the anterior and midaxillary line in the fifth and sixth intercostal spaces, respectively. Another two 1-cm incisions were made medial to the scapula. A Veress needle was placed through the midaxillary line incision and CO₂ was insufflated to a pressure of 10 mm Hg while the right lumen of the endotracheal tube was opened to air, thus collapsing the right lung. After trocar insertion of an instrumentation port (Autosuture Surgiport; U.S. Surgical Corp, Norwalk, CT), the video element was inserted into the thoracic cavity. All trocars except this first one were inserted under direct thoracoscopic visualization. The right lower lobe was found to be adherent to the anterior surface of the cyst, and these adhesions were taken down by a combination of blunt and cautery dissection. The lung was then retracted with a clamp (Autosuture Endobabcock; U.S. Surgical Corp) to expose the anterior surface of the cyst. A Veress needle was then advanced into the cyst and 240 mL of thick, green mucoid material was removed. Cultures for aerobic and anaerobic bacteria, fungus, and acid-fast bacillus were obtained. After the aspiration, the

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A



B

Fig 1. (A) Posteroanterior chest roentgenogram demonstrating subcarinal bronchogenic cyst with lateral displacement of right bronchus. (B) Chest computed tomographic scan demonstrating 10-cm fluid-filled mediastinal cyst with compression of bronchus intermedius.

cyst wall was grasped with a clamp, and using blunt and cautery dissection, the posterior aspect of the cyst was then dissected off the esophagus and vagus nerves. Once the lateral cyst wall had been dissected as far medially as the right main pulmonary artery and superior pulmonary vein, the cyst wall was resected using the cautery. This left a small portion of epithelial-lined cyst wall covering the underside of the right pulmonary artery, the carina, and the posterior left atrial aspect of the pericardium. The wound was liberally irrigated with a 1% bacitracin solution, and hemostasis was obtained with the cautery. Two chest tubes were inserted through the anterior and mid-axillary trocar sites. These tubes were left in the anterior and posterior aspects of the pleural cavity, and the lung was then reexpanded. The operative time excluding anesthesia was 3 hours 45 minutes, and estimated blood loss was 400 mL.

The patient was extubated the following morning. A postoperative chest roentgenogram showed that the mass was gone and a small air fluid level remained in the subcarinal area. The chest tubes were removed on the second postoperative day, and the patient was discharged home on the third postoperative day and resumed his normal activities on the same day. All intraoperative cultures of the cyst wall and fluid yielded no growth.

In the 9 months since discharge, no respiratory tract infections have occurred, and chest roentgenogram reveals no evidence of cyst recurrence.

Comment

Video thoracoscopy is a relatively new technique that presently comprises but a small portion of the practice for most thoracic surgeons. Although video thoracoscopy has been used in the past mainly for exploratory and diagnostic purposes, recently practitioners have broadened the utilization of this technique for bullectomy [1], thoracic sympathectomy [2], empyema drainage [3], lung biopsy [4], and pericardial drainage [5]. The patient presented herein carried a very high operative risk no matter what approach was chosen, as the risk of general anesthesia alone was clinically significant. Although there is certainly a risk of fluid reaccumulation and cyst recurrence after this subtotal resection, this minimally invasive approach seemed most appropriate for this elderly and debilitated gentleman. This thoracoscopic approach was certainly less invasive and morbid than a thoracotomy, which yields major postoperative pain and ventilatory compromise (with a resultant increased risk of pneumonia and respiratory insufficiency). In addition, the time of hospitalization and recuperation was far shorter than would have been the case with a major invasive procedure.

As new techniques evolve and appropriate surgical instrumentation is developed, it is likely that more procedures will prove amenable to this approach. However, as noted in a recent editorial [6], it is important that physicians not allow themselves to be seduced into surgical compromises because of apparent technologic advances. For example, although minimal resections for bronchogenic carcinoma can be accomplished using video thoracoscopy, it will probably prove to be appropriate only for a small number of lung cancer patients [4]. It is important not to allow the desirability of minimally invasive surgery to result in an operation that may compromise the long-term outcome. Before time-tested practices and procedures are abandoned, prospective studies documenting the efficacy of the thoracoscopic approach must first be reported. The organization of a multiinstitutional cooperative study group is already underway and will be a major step toward this goal (J LoCicero III; personal communication).

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REVIEW OF RECENT BOOKS

Cardiac and Noncardiac Complications of Open Heart Surgery: Prevention, Diagnosis and Treatment

Edited by Morris N. Kotler, MD, and Anthony Alfieri, DO
Mt. Kisco, NY, Futura, 1992
418 pp, illustrated, \$62.00

Reviewed by Joe W. R. Bolton, MD

This book represents a good medical overview of the preoperative evaluation and postoperative recognition and treatment of the complications of cardiac operations. It is well-referenced and up-to-date, and contains excellent tables, which are aptly discussed in the text. The book admittedly does not contain information concerning the heart transplant patient or the congenital heart patient. It also does not discuss intraoperative complications but limits itself to the medical issues outside the operating suite.

The first chapter presents a superb discussion of the indications for surgical and medical therapy for patients with coronary artery disease. It is based predominantly on a review of the results of the Coronary Artery Surgery Study, the Veterans Administration Cooperative Study, and the European Coronary Surgery Study. Risk factors, survival data, and patency rates are

all discussed in a logical and concise fashion, leading to current recommendations for therapy.

Similarly, the final chapter concerning the prevention of progressive atherosclerosis in coronary artery bypass patients addresses a problem not often discussed in books on the complications of cardiac operations. It reviews the pathophysiology of coronary atherosclerosis in the preoperative and postoperative patient and discusses the current modalities for the prevention and regression of coronary atherosclerosis including dietary changes, drug therapy, and lifestyle changes such as exercise and stress management.

The intervening chapters offer clear, succinct discussions on issues ranging from cardiac complications such as cardiac dysrhythmias and low output syndromes to noncardiac complications such as infections, gastroenterologic, endocrine, hematologic, pulmonary, neurologic, psychiatric, and renal complications.

Overall, the text represents an up-to-date, well-referenced, and well-organized work. It is certainly an easy to read, useful reference for the intensive care unit, postoperative ward, and physician involved in the care of those adult patients undergoing cardiac operations.

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Combined Thrombolytic Therapy for Prosthetic Mitral Valve Thrombosis

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Prosthetic valve thrombosis is associated with high mortality. The treatment of choice remains operation. This is a case report of the successful combination therapy of tissue plasminogen activator and urokinase for an isolated thrombosed prosthetic mitral valve in a postpartum patient in whom operation was thought to carry an

unacceptable risk. Combined thrombolytic therapy or therapy with a single agent with a long half-life and a prolonged infusion time is suggested as an emergent treatment option for prosthetic mitral valve thrombosis.

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Prosthetic cardiac valve thrombosis, which has an incidence rate of 0.5% to 6%, is associated with a high mortality (60% to 80%) [1]. The mechanism for obstruction represents a spectrum between chronic pannus formation [2] and acute or subacute thrombosis. The location of the valve prosthesis seems to be important in terms of frequency of thrombosis, with the tricuspid valve site carrying the highest percentage (up to 20%) of thrombosis [3], followed by the mitral valve and the aortic valve, respectively. The mortality for an emergency operation depends on different parameters, such as age and left ventricular function, and varies between 35% to 55% for the critically ill patient and 4.7% for very stable patients in a good functional class. For the past two decades there have been numerous sporadic reports on thrombolytic therapy used either as a temporizing measure for semielective operation in lower risk patients or as a curative process. Most case reports of tissue plasminogen activator (TPA) have been for cases of prosthetic tricuspid valve thrombosis [4]. To the best of our knowledge only 1 case has been reported of the use of TPA in association with streptokinase in a patient with tricuspid and mitral valve thrombosis [5]. This is a case report of the probable failure of TPA followed by a successful rescue administration of urokinase for an isolated thrombosed prosthetic mitral valve in a postpartum patient at extremely high risk for operation.

A 16-year-old black girl was admitted to the coronary care unit at Parkland Memorial Hospital for postpartum congestive heart failure. When she was 8 years old, pancarditis had developed secondary to rheumatic heart disease. Mitral insufficiency later developed with symptoms of left ventricular dysfunction over the next 3 years, leading to mitral valve replacement with a Medtronic-Hall valve

(27-mm) when the patient was 11 years old. At that time, cardiac catheterization also showed mild to moderate aortic insufficiency. Three months later she had severe orthopnea and dyspnea with evidence of left and right ventricular dysfunction on physical examination. An echocardiogram revealed four-chamber dilatation, moderately depressed left and right systolic ventricular function, and severe aortic insufficiency without mitral regurgitation. She underwent aortic valve replacement with a St. Jude valve (23-mm) with a good postoperative recovery.

Despite recommendations to the contrary, the patient became pregnant and refused abortion. Subcutaneous heparinization was recommended as the primary method of anticoagulation for the remainder of her pregnancy. At the 33rd week of pregnancy, she was hospitalized after having contractions, increased blood pressure, 2⁺ proteinuria, dyspnea, and evidence of inadequate anticoagulation. The diagnosis of preeclampsia was suggested, and the patient was started on a regimen of intravenous magnesium and intravenous heparin. Physical examination showed no evidence of congestive heart failure, but chest roentgenogram showed cardiomegaly and pulmonary vascular redistribution. Opening and closing clicks of both valves were distinctly heard. Anticoagulation was stopped for the delivery and resumed 6 hours after.

Oliguria developed and the patient was transferred to the coronary care unit for increased tachypnea, acidosis, and pulmonary edema. At that time she had a muffled mitral valve closing click and no opening click. An emergency echocardiogram revealed severe left ventricular systolic dysfunction, pulmonary hypertension, severe tricuspid insufficiency, and moderate aortic insufficiency. A probable mitral valve thrombosis was suggested, and the mitral valve area was calculated by the pressure half-time method as 0.6 cm², decreased from 1.9 cm² 6 months before the admission. A transesophageal echocardiogram showed a mass consistent with a thrombus on the mitral prosthetic valve and very poor left ventricular systolic function.

A surgical consult suggested that the operative mortal-

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ity was prohibitive, and thrombolytic therapy was elected. A pulmonary arterial catheter revealed a cardiac output of 1.78 L/min by thermodilution (1.9 L/min by Fick equation), a pulmonary capillary wedge pressure of 30 mm Hg, and a pulmonary systolic pressure of 100 mm Hg. Tissue plasminogen activator was given through the pulmonary artery catheter as a 20-mg bolus, then 50 mg for the first hour and 30 mg for the second hour. After the TPA infusion the patient sustained serious vaginal bleeding requiring vasopressin and cryoprecipitate. Her hemodynamic status improved (cardiac output of 5 L/min) with decreased pulmonary hypertension. Her prosthetic mitral valve opening click remained absent several hours after thrombolytic therapy despite adequate heparinization after controlling the vaginal bleeding. An echocardiogram revealed an ongoing mitral valve thrombus. A few hours later, the patient experienced further hemodynamic compromise requiring intubation. In view of her previous history of rheumatic heart disease, streptokinase was thought to be relatively contraindicated and therefore urokinase was infused at 4500 U/kg over 12 hours. There was progressive improvement in her hemodynamics and the mitral valve opening click was again audible on physical examination at the end of the infusion. An echocardiogram revealed a mitral valve area of 1.2 cm² and the absence of thrombus. Fluoroscopy confirmed reduced opening angle of the mitral prosthetic valve consistent with chronic pannus formation.

A week later while receiving warfarin only (prothrombin time of 19 seconds) she experienced nystagmus and diplopia, which resolved after a few hours. Subsequently she had another transient ischemic attack with right-sided weakness and dysarthria. A high-resolution computed tomographic scan revealed cerebral emboli. However, surgical intervention was still thought to carry an unacceptable risk and the patient was maintained on heparin followed by warfarin with a prothrombin time maintained at 22 to 25 seconds without other embolic evidence. Her predischARGE ejection fraction was 0.50, and the patient remained asymptomatic at 6-month follow-up.

Comment

The treatment of choice for prosthetic valve thrombosis remains operation. However, the very poor left ventricular systolic function of our patient placed her at an unacceptable risk for a third cardiac operation. The postpartum state and related bleeding condition prompted us to choose TPA because this agent has been associated with less systemic fibrinolysis. Low-dose TPA has recently been advocated for tricuspid valve thrombosis with good results, but because TPA was never used as a sole thrombolytic agent for prosthetic mitral valve thrombosis, we chose to administer a full dose of TPA over a 2-hour period. The transient improvement followed by hemodynamic deterioration confirm that a short course of TPA or TPA as the only thrombolytic agent may contribute to but is probably not sufficient for successful prosthetic mitral valve thrombolysis. The consistent improvement after urokinase administration points toward the justification

for a thrombolytic agent with a long half-life or perhaps an extended TPA infusion as suggested for the treatment of tricuspid valve thrombosis [6]. This could have potentially more thrombolytic effect, but this remains unproven for mitral valve thrombosis. Even the long half-life of streptokinase or urokinase infused over 12 hours does not necessarily guarantee success. Indeed, 7 of 26 patients in the series reported by Ledain and associates [7] required a dose of another thrombolytic agent. So it appears that 12 hours is a minimum infusion time for a mitral valve thrombosis and that an extension to 24 to 36 hours [7] should be considered.

Our patient probably had a chronic pannus formation, as shown by the reduced opening angle of the mitral valve after thrombolysis. The hypercoagulable state of the post-delivery period and the termination of heparin administration before delivery have precipitated the formation of acute thrombosis superimposed on a probable chronic pannus. The latter has been shown to be present in up to 46% of cases of any valve obstruction [8]. In this case the pannus may have developed in the long period of inadequate anticoagulation in this noncompliant patient. As pointed out by Deviri and associates [8], not all patients with subacute valve obstruction are symptomatic. The decision to debride the pannus or replace the valve is debatable, and the early surgical mortality rate for prosthesis declotting and excision of the pannus is comparable with that of valve prosthesis replacement [8]. In our case the patient refused operation.

It has been suggested that thrombolytic therapy should not be used for left-sided thrombosis due to high risks of systemic embolization [9]. Indeed, this risk ranges from 15% and 25%, although most of the patients will recover spontaneously or with further thrombolysis because these are typically microemboli and rarely associated with permanent sequelae. A high dose of warfarin to maintain the prothrombin time between 22 and 25 seconds as suggested by our case report might be beneficial in the first few weeks after prosthetic valve thrombolysis.

In summary, TPA as a sole thrombolytic modality may be insufficient for prosthetic mitral valve thrombosis, but combined with streptokinase [5] or with urokinase it may be curative or at least provide hemodynamic stability and improvement in cardiac function for the patients in whom operation is associated with an excessive mortality risk.

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Free Splenic Artery Used in Aortocoronary Bypass

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Many alternative bypass conduits for coronary revascularization have been used since the introduction of the saphenous vein. The internal mammary artery has demonstrated superior long-term patency rates compared with vein grafts. Other arterial grafts previously investigated include the right gastroepiploic artery, inferior

epigastric artery, radial artery, and splenic artery. This case reports bypass using a free splenic artery and a pedicled right gastroepiploic artery, each with successful postoperative patency.

(*Ann Thorac Surg* 1993;55:162-3)

Aortocoronary bypass grafts have extremely high patency rates with the use of the internal mammary artery (IMA). Use of the saphenous vein as an arterial conduit also provides for excellent revascularization. Because of the need for additional conduits, particularly in redo revascularization cases, alternative arterial grafts have been investigated including: (1) right gastroepiploic artery (RGEA), (2) inferior epigastric artery, (3) radial artery, and (4) splenic artery. The splenic artery has been used only as a pedicled graft, whereas the IMA and RGEA arteries have been used both as a free graft and as a pedicled graft [1, 2]. The radial artery and inferior epigastric artery for obvious reasons have only been used as a free graft [3-5]. Reported is a case in which the splenic artery as a free graft and an in-situ RGEA were used with successful postoperative patency.

The patient was a 67-year-old woman who came to the emergency room complaining of chest pain, dyspnea, and orthopnea. Medical history revealed the patient had coronary artery bypass grafting four times—the two most recent with cadaver veins. Coronary angiography showed thrombosis of the recent cadaver vein grafts to the left anterior descending and the obtuse marginal arteries. During the angiography the patient complained of rest angina requiring intraaortic balloon pump insertion. Thrombolytic therapy was attempted without success. No infarction had occurred, and the left ventricular ejection fraction remained 0.28.

The patient was taken to the operating room for revascularization of the left anterior descending artery and the obtuse marginal artery. During the previous four operations, all greater saphenous veins, lesser saphenous veins, cephalic veins, inferior epigastric arteries, and both IMAs had been used or determined to be unsuitable for use. Cadaver veins had been used for the two most recent bypass procedures. Also, the patient had no palpable radial pulses in either arm, thereby eliminating this vessel as a potential conduit. Multiple angioplasties had also

been attempted with dismal results. Aortocoronary bypass grafting was performed using the RGEA anastomosed to the obtuse marginal artery and the free splenic artery to the left anterior descending artery. Excellent Doppler pulses were present for both grafts.

The patient's postoperative course was complicated by pneumonia, bacteremia, and a urinary tract infection. The patient at 7 months is asymptomatic and has demonstrated no clinical signs of ischemia. An adenosine thallium stress test was obtained postoperatively and demonstrated no areas of reversible ischemia. Because of severe peripheral vascular disease, it was decided not to repeat coronary angiography. In fact, since the operation the patient has required an axillo bifemoral artery bypass graft.

Comment

Since the origin of coronary revascularization, surgeons and cardiologists have searched for the optimal vascular conduit. The saphenous vein graft has been the primary graft used. However, more reliable grafts have been desired because patency rates for veins are 70% to 80% in men and approximately 10% to 15% lower in women [6].

Thus far the optimal bypass graft has been the IMA [6]. Although technically more difficult, the IMA provides superior patency compared with any other graft thus far investigated. The Cleveland Clinic has recommended that the IMA be the first choice for coronary revascularization. The RGEA has also been investigated, with two studies demonstrating excellent early patency of RGEA when used as a pedicled or free graft [7, 8]. Experience with the inferior epigastric artery is also limited, and current literature concerning the free radial artery demonstrates approximately 33% patency [3, 4].

Edwards and associates [1] in 1973 employed the splenic artery as an in-situ graft passing through the membranous portion of the diaphragm and anastomosed to the distal right coronary artery. The splenic artery was mobilized behind the pancreas at the junction of the body and tail with obligatory splenectomy. Two postoperative splenic artery angiograms demonstrated widely patent anastomosis. Potential disadvantages of using the splenic artery were noted to be its tortuous course and larger

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diameter as compared with the right coronary artery. Edwards and associates [1] did not find these to be major problems.

A free splenic artery bypass graft to the left anterior descending and a pedicled RGEA bypass graft to the obtuse marginal artery were performed in our patient. The midsternotomy incision was extended to the umbilicus. After the right gastroepiploic artery pedicle was freed, the lesser sac was entered. The splenic artery was identified along the upper border of the pancreas. Beginning at the middle of the artery, the dissection proceeded medially to its origin from the celiac axis. Multiple small branches pass from the splenic artery to the pancreas, and each was carefully ligated. Also, great care was taken to avoid any injury to the pancreas. Next the dissection proceeded laterally. Once the tail of the pancreas was reached the spleen was freed from its lateral attachments. The short gastrics were divided, and the artery was divided after branching occurred. An obligatory splenectomy was performed. The original intent was to use the splenic artery as an in-situ bypass graft for the obtuse marginal artery; however, the length was inadequate. It was therefore divided at the celiac axis and used as a free graft to the anterior descending vessel. Four technical aspects of using this vessel merit mention. First, the majority of the tortuosity can be straightened by dividing the surrounding tissue. Second, the intima was extremely friable near the splenic hilum, necessitating meticulous suturing. Third, the splenic artery possessed diffuse calcification, which made the anastomosis more difficult, but possible. Finally it must be emphasized that meticulous dissection should be performed at the upper surface of the

pancreas to avoid any injury of this organ and potential pancreatitis.

In conclusion, this patient represents an increasing number of complex redo revascularizations that all surgeons will face. The splenic artery is offered as a potential conduit in an extremely desperate situation. Short length of the splenic artery will limit its use to the posterior descending vessel as an in-situ graft and to the anterior descending vessel or diagonal branch as a free graft. The IMA and saphenous vein graft remain the conduits of choice for most patients.

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Treatment of Incessant Reciprocating Atrioventricular Tachycardia by a Closed Heart Surgical Technique

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The case of a 40-year-old woman having disabling symptoms of incessant atrioventricular reciprocating tachycardia is reported. She underwent surgical therapy by a closed heart technique. Operative technique and the advantages of the epicardial approach in the present case are detailed.

(*Ann Thorac Surg* 1993;55:164-6)

The permanent form of junctional reciprocating tachycardia is considered to be a variant of preexcitation syndromes. This incessant tachycardia with a normal QRS was first described by Coumel and associates in 1967 [1]. The arrhythmia is a reciprocating tachycardia with the antegrade limb in the atrioventricular node and a retrograde limb with decremental functional properties in the septal ventriculoatrial area. It is associated with severe cardiac dysfunction and is poorly responsive to pharmacologic treatment. The current therapeutic modalities include destruction of the retrograde limb by radiofrequency catheter ablation [2] and surgical section by an endocardial approach [3, 4] or by a closed heart technique [4, 5].

Because, to our knowledge, surgical ablation of the accessory pathway using an epicardial approach without cardiopulmonary bypass has been reported in only 8 patients [4, 5], we describe a further patient operated on successfully with the latter technique.

A 40-year-old woman was referred with a 20-year history of rapid heart rate. She complained of palpitations, tiredness, and limited physical activity. Conventional medical therapy including digoxin, β -blocking agents, and amiodarone was unsuccessful in controlling symptoms. The standard electrocardiogram showed the classic features of permanent junctional reciprocating tachycardia, namely, a 1:1 atrioventricular relationship with a marked negative retrograde P wave in leads II, III, and aVF. The P wave occurred closer to the succeeding QRS complex than the preceding one. Holter monitoring demonstrated incessant tachycardia with rates varying between 148 and 90 beats/

min (average, 108 beats/min) and only brief interludes of sinus rhythm. There was typically a pause followed by one sinus cycle before resumption of tachycardia. Electrophysiologic study demonstrated an orthodromic atrioventricular reentry using a concealed accessory pathway with decremental conduction properties. The site of earliest retrograde atrial activation during reciprocating tachycardia was at the coronary sinus orifice. Isotopic left ventricular ejection fraction was 0.30 at rest and increased to 0.37 with a workload of 90 W.

At operation, the heart was exposed through a median sternotomy. Intraoperative cardiac mapping was performed using a 24-electrode epicardial band array and a computer-assisted mapping system (Bard Cardiac Mapping System; Bard, Billerica, MA). The pathway was localized to the posteroseptal region (Fig 1). The operation was performed on the normothermic beating heart without the use of cardiopulmonary bypass, following the technique described by Guiraudon and associates [6]. The right ventricular inferior wall was retracted upward. The epicardium of the right inferior fat pad was incised along its ventricular limits, and the incision was extended medially to the coronary sinus anteriorly. The right coronary artery and its branches were exposed (Fig 2). Further mobilization of the right atrioventricular fat pad gave exposure to the posterior superior process of the left ventricle. Permanent cardiac rhythm monitoring was provided during the procedure, and tachycardia disappeared permanently during dissection of the origin of the posterior descending artery. Concomitantly, we observed an increase in systemic pressure and a decrease in central venous pressure (Fig 3). A cryoprobe 5 mm in diameter (CCS-200; Frigitrionics, Shelton, CT), cooled to -60°C for 2 minutes for each application, was used to complete the ablative procedure. Control mapping showed the absence of premature activation of the posteroseptal area.

The patient was extubated immediately after the procedure and had an uneventful recovery. Pairs of temporary pacing wires implanted over each cardiac chamber were used for the postoperative stimulation study, which demonstrated absence of retrograde conduction over the accessory pathway. Six months after operation, this patient is asymptomatic and fully active. Left ventricular isotopic ejection fraction determined at rest was 0.52.

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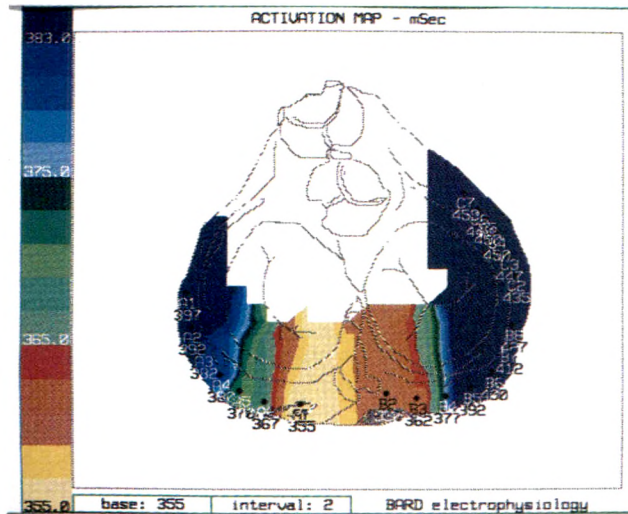


Fig 1. Atrial activation map during spontaneous incessant tachycardia. The earliest atrial activation appears in the region near the coronary sinus os and is represented by yellow. The numbers represent the ventriculoatrial conduction times, with the shortest value of 355 ms at the coronary sinus os.

Comment

Division of accessory pathways with a technique that avoids aortic cross-clamping and cold cardioplegic arrest may improve surgical results. Comparison of the endocardial versus epicardial approach in the surgical treatment of the Wolff-Parkinson-White syndrome suggested that the epicardial approach could be advantageous for interrupting accessory pathways of the posterior septal region [7].

In particular, the endocardial approach to the posteroseptal area may induce inadvertent atrioventricular block

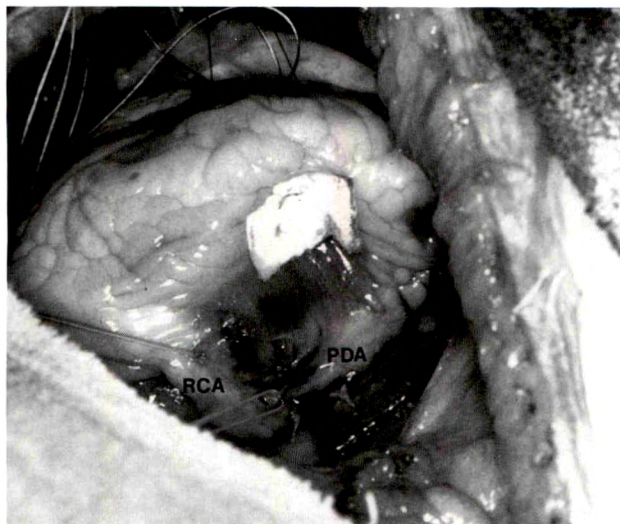
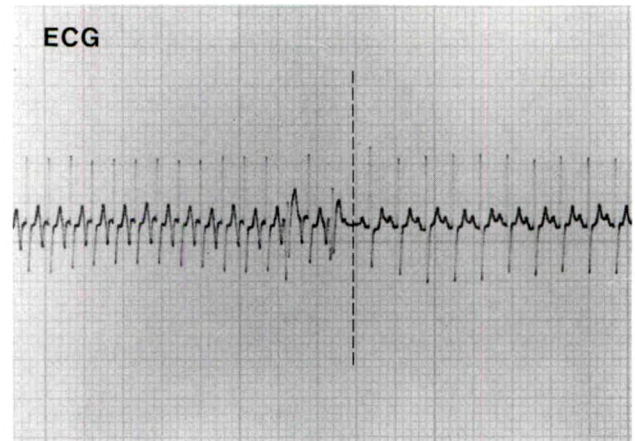
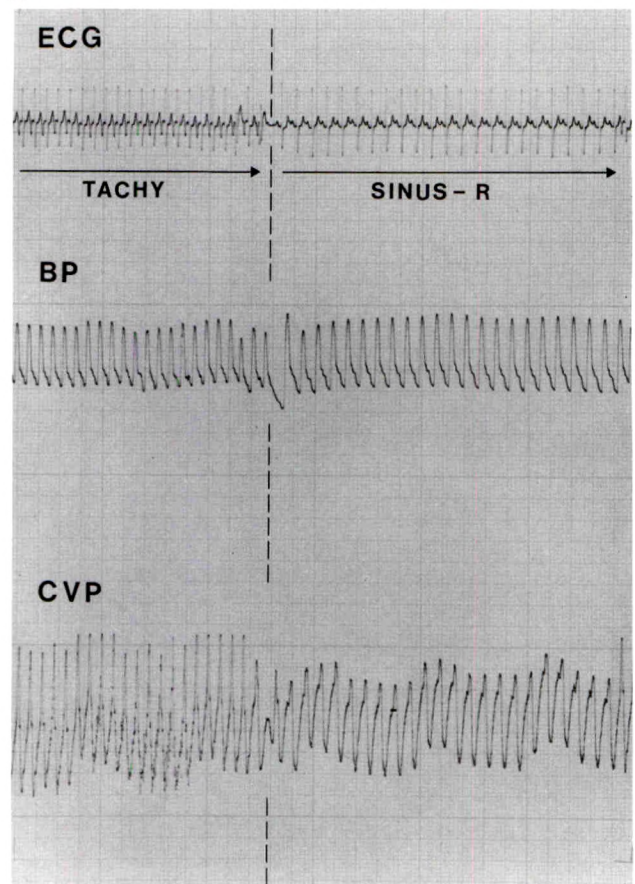


Fig 2. Operative view of the dissection of the posteroseptal pathway. The right ventricular inferior wall is retracted upward with a pledget-supported suture. The right coronary artery (RCA) and the posterior descending artery (PDA) are isolated on vessel loops.



A



B

Fig 3. (A) Tachycardia and negative retrograde P wave disappeared permanently during dissection of the origin of the posterior descending artery. (B) A concomitant increase in systemic pressure (BP) and decrease in central venous pressure (CVP) were observed. (ECG = electrocardiogram; R = rhythm; TACHY = tachycardia.)

[8]. The closed heart technique performed on a normothermic beating heart prevents permanent atrioventricular block by permitting continuous control of atrioventricular conduction during dissection and cryoablation. In the present case, by monitoring the cessation of the tachycar-

dia, we were able to locate exactly the accessory pathway and concentrate our dissection and cryoablation on that area.

With the increasing availability of radiofrequency catheter ablation techniques, operation for accessory pathways will be realized more selectively. We believe that the posterior septal epicardial approach is well adapted to the difficult cases of failed catheter ablation.

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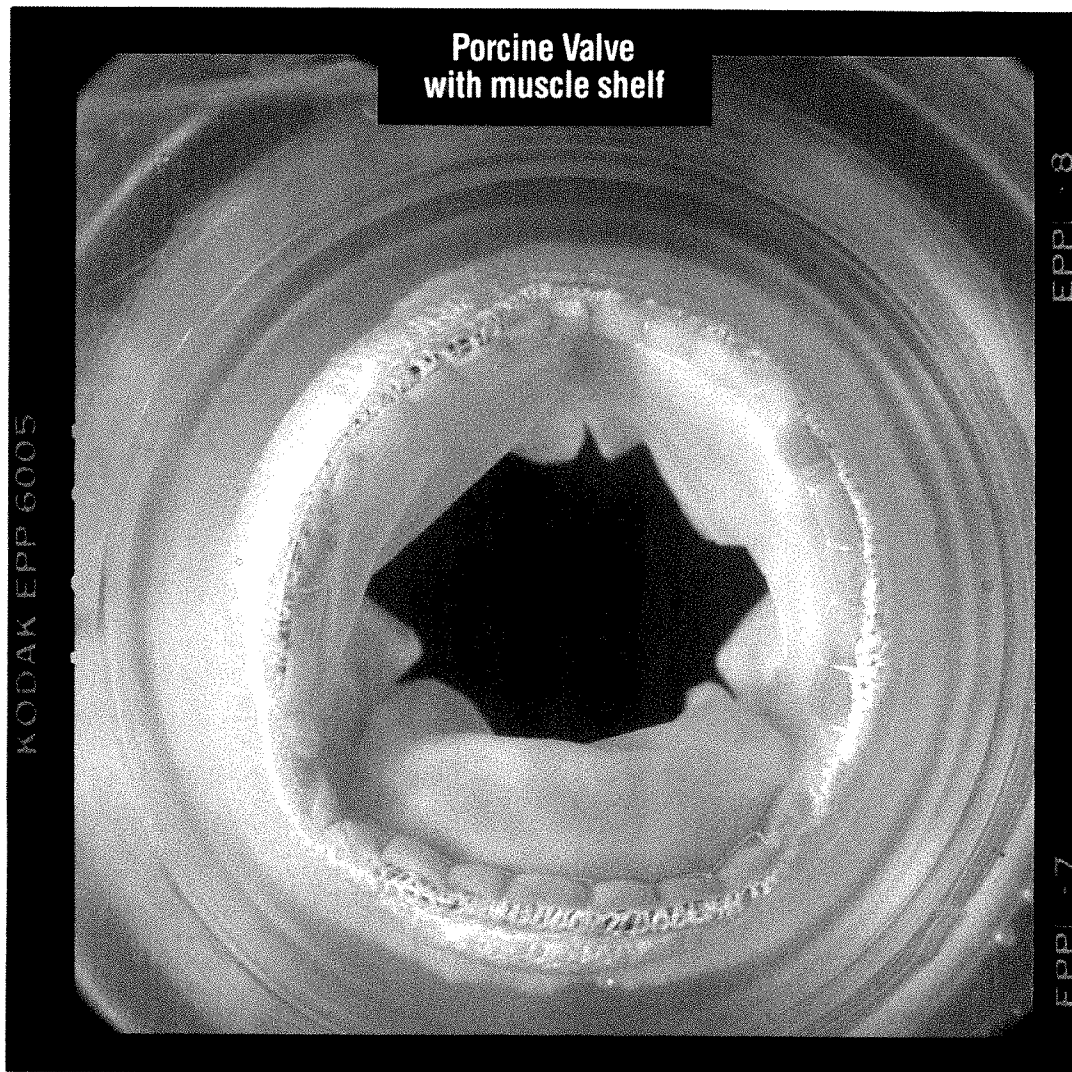
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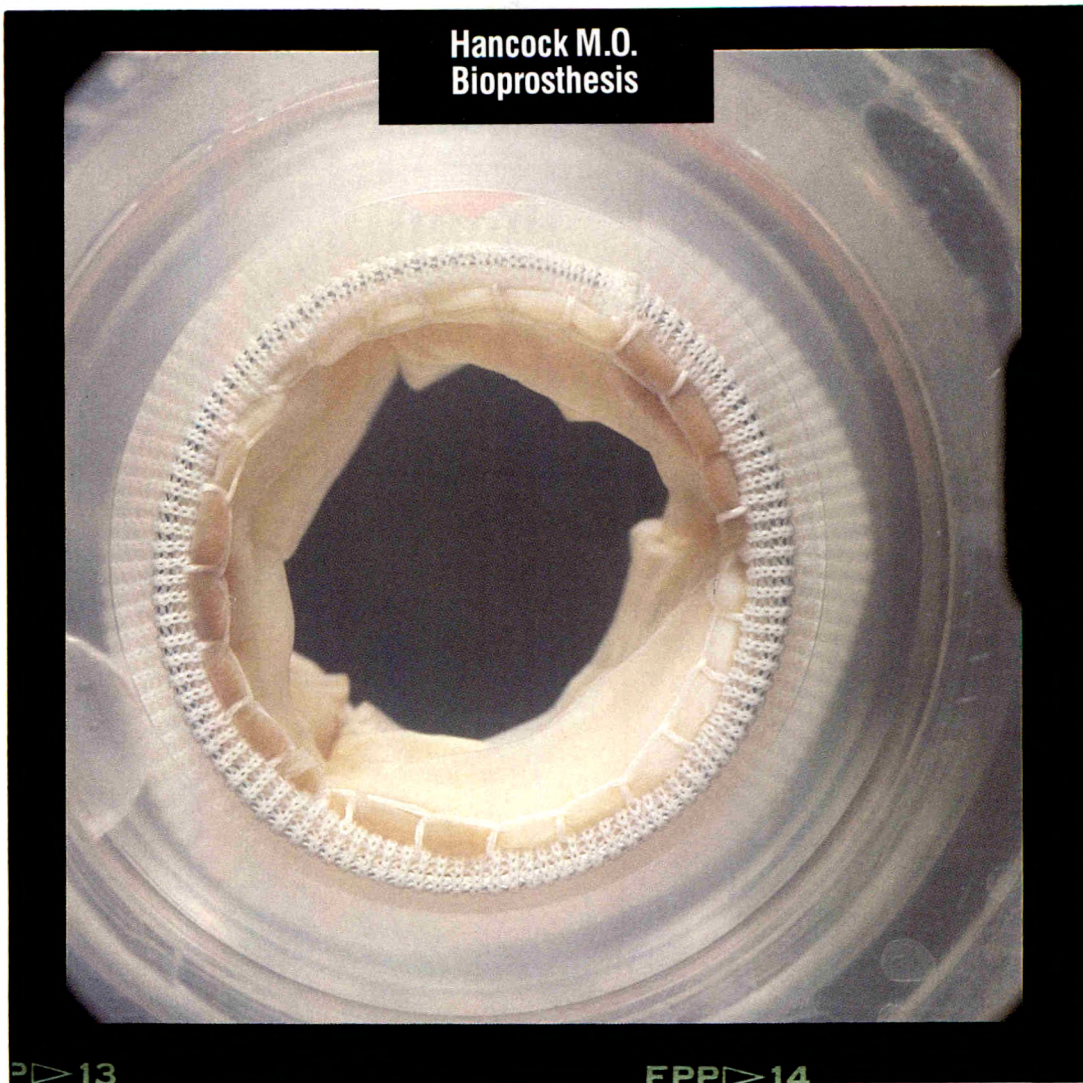
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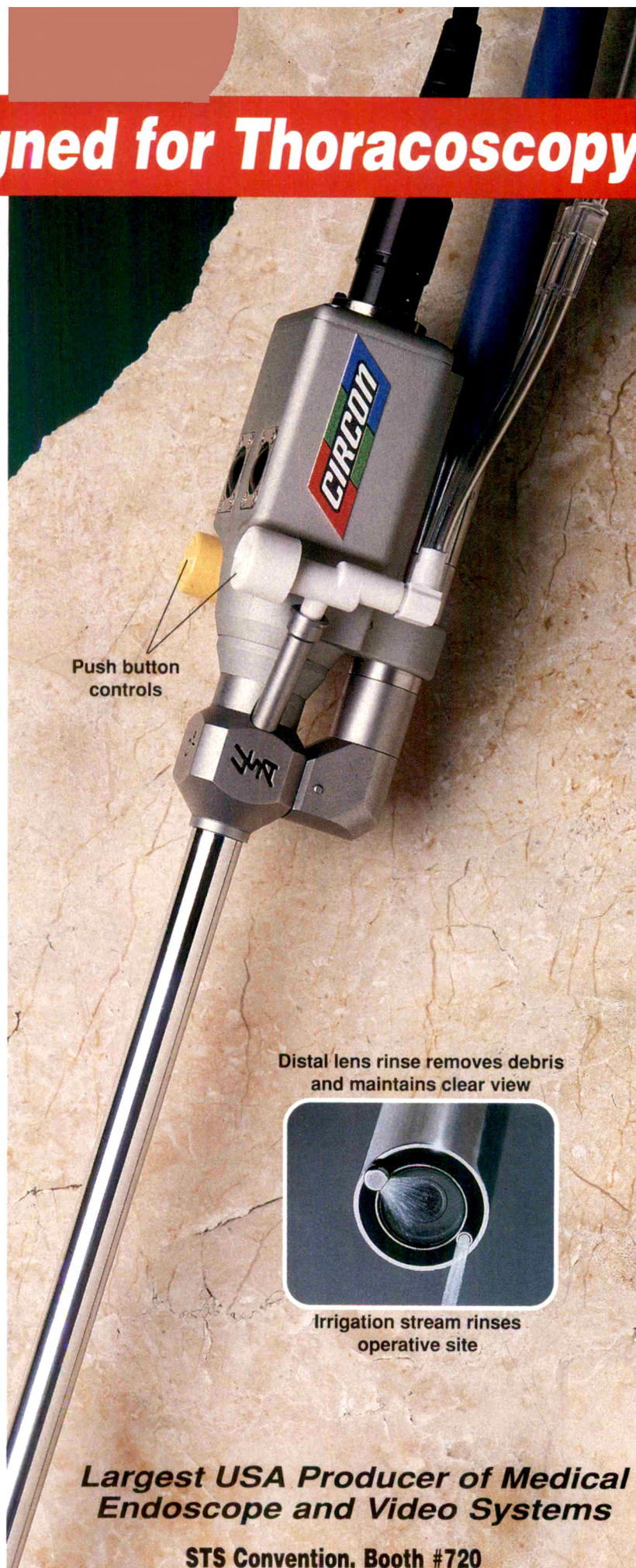
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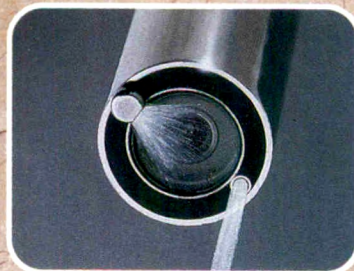
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Management of a Mediastinal Cyst Causing Hyperparathyroidism and Tracheal Obstruction

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A 78-year-old man with a history of parathyroidectomy presented with hyperparathyroidism and tracheal obstruction. After excision of the mediastinal parathyroid cyst, his symptoms were completely relieved. The diagnosis, investigations, and management are discussed.

(*Ann Thorac Surg* 1993;55:167-8)

Mediastinal parathyroid cysts are rare; only 17 cases have been reported in the literature to date. Only 3 of those had associated hyperparathyroidism [1-4]. Multiple parathyroid adenomas are also extremely rare [5, 6]. This report presents a case of hyperparathyroidism with two cervical parathyroid adenomas and a hyperfunctioning mediastinal parathyroid cyst causing tracheal obstruction and mental depression.

A 78-year-old man was referred to our unit in January 1991 with dyspnea and stridor. Five years before this admission, he had a variety of psychiatric problems, ranging from depression to agitation, and also had recurrent urinary tract infection. He was initially treated with antidepressants and antibiotics.

Ten months later, he was readmitted with a fracture of his pelvis after a fall. A chest radiograph this time showed a superior mediastinal mass (Fig 1), and a radiograph of the abdomen revealed a right renal calculus. He was also found to have a raised serum calcium level of 3.27 mmol/L (normal, 2.2 to 2.6 mmol/L) and a raised parathormone level of 13.41 ng/mL (normal, 0.4 to 1.3 ng/mL). A thallium/technetium 99m scan of the neck and the upper mediastinum failed to show hyperfunctioning parathyroid tissue. He declined to have an operation and was treated with calcitonin and antidepressants.

One year later, he agreed to have surgical exploration of his neck. At the operation, left superior and inferior parathyroid adenomas were removed and a normal right inferior parathyroid gland was preserved. The right superior parathyroid gland could not be found. Biopsies of the mediastinal cyst did not show any evidence of parathyroid tissue. Postoperatively, the serum calcium and parathormone levels were lower (calcium, 3.16 mmol/L;

phosphate, 0.6 mmol/L; parathormone, 4.76 ng/mL) but still remained above the normal range. The patient refused to have further operation.

Two years later, dyspnea and upper respiratory tract stridor led to his current admission to our unit. A computed tomographic scan showed the previous cystic lesion, which had increased in size and was now causing severe tracheal compression (Fig 2). A repeat thallium/technetium scan did not show any enhanced uptake in the mediastinum. At operation, through a right dorsolateral thoracotomy incision, a cyst 8 cm in diameter was located in the posterosuperior mediastinum with a pedicle arising from the right side of the neck. The cyst was excised in toto. The right recurrent nerve could not be identified because of dense adhesions. Microscopically, the mass consisted of dense fibrous and fibrofatty tissue but was devoid of any epithelial lining, with occasional lymphoid foci and several islands of parathyroid tissue. There were clumps of red cells and old blood clots on the inner lining of the cyst indicating previous hemorrhage into the cyst.

After the operation, the serum calcium and parathormone levels returned to normal (calcium, 2.3 mmol/L; parathormone, 1 ng/L). He had mild recurrent nerve palsy, which was treated by Teflon injection with a good result. His mental depression was very much improved.

Comment

Mediastinal parathyroid cysts infrequently occur and rarely cause tracheal obstruction. It is very unusual for these cysts to cause hyperparathyroidism, particularly in association with other adenomas. Multiple parathyroid adenomas are very rare indeed. Wang [5], in his review of 500 cases of hyperparathyroidism, did not find a single patient with multiple adenomas. It is generally accepted that hyperfunctioning adenoma suppresses the other glands, thereby preventing the development of other parathyroid adenomas in the same patient. This certainly was not the case in our patient; not only did he have two cervical adenomas but he also had a mediastinal cyst containing hyperfunctioning parathyroid tissue that continued to secrete enough parathyroid hormone to maintain symptoms of hyperparathyroidism even after successful excision of the cervical adenomas.

Preoperative localization of these cysts is very important. In our patient, there was a strong suspicion of the mediastinal cyst being parathyroid in origin, but the

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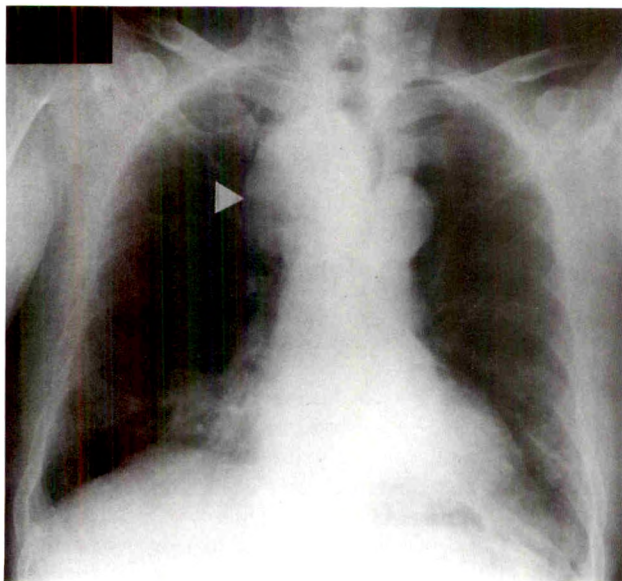


Fig 1. Chest radiograph showing a large, round lesion in the superior mediastinum pushing the trachea to the left.

thallium/technetium scan and the biopsy of the cyst were negative. The reported sensitivity of thallium/technetium scan ranges from 92% to 76% [6]. Biopsy of the cyst was not helpful in establishing the diagnosis because islands of parathyroid cells were not homogeneously situated in the wall. Therefore an exploratory operation should be

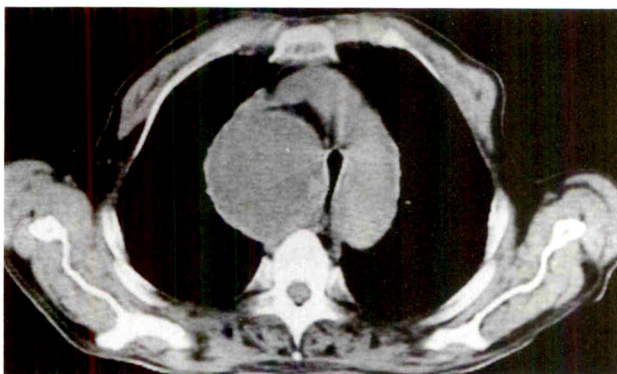


Fig 2. Computed tomographic scan demonstrating a large cystic lesion causing severe tracheal compression at the level of the superior mediastinum.

performed on clinical grounds if investigations fail to show functioning parathyroid tissue.

The inferior parathyroid glands develop from the third pharyngeal pouch with the thymus. In the ectopic position, they are usually located in the superior mediastinum, whereas the superior glands arise from the fourth pharyngeal pouch and are situated between the superior edge of the larynx and the lower pole of the thyroid gland [7]. In our patient, the right superior parathyroid could not be located and the cyst was in the right posterior mediastinum with the pedicle arising from the right side of the neck. These findings would suggest that this mediastinal parathyroid cyst could have been the ectopic right superior parathyroid gland, which had originated in the neck and had descended into the posterior mediastinum. Enlargement of the cyst leading to tracheal obstruction could have been caused by hemorrhage into the cyst as documented by histological findings.

Although depression is a known complication of hyperparathyroidism, this case is unusual in that depression was associated with a hyperfunctioning mediastinal parathyroid cyst.

It is important that cystic lesions of the mediastinum should be removed for diagnosis, particularly in a patient who has an endocrine abnormality.

We would like to express our gratitude to Dr J. B. Kershaw, Dr H. P. Bury, and Dr P. Martin for their invaluable help with histopathological and biochemical diagnostic work.

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Multiple Tumor Emboli After Pneumonectomy

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Systemic arterial tumor embolization is a rare complication after pulmonary resection. It may occur with primary or metastatic pulmonary malignancies, and is more frequently associated with pneumonectomy than with lesser pulmonary resections. Despite the rarity of this

complication, tumor emboli should be considered in the etiology of extremity, cerebral, or multiorgan ischemia occurring during the perioperative period in patients undergoing pulmonary resections for malignancy.

(Ann Thorac Surg 1993;55:169-71)

Massive systemic tumor emboli complicating pulmonary resection for bronchogenic carcinoma are rare. Similarly, tumor embolization to the cerebral circulation is an uncommon event after lung resection and often not considered as the cause of stroke in the cancer patient [1, 2]. We present our experience with a patient who underwent an extended pneumonectomy for a large, centrally located, bronchogenic tumor.

A 55-year-old man presented with hemoptysis and with right chest and back pain. Physical examination was remarkable only for decreased breath sounds in the lower right hemithorax. Chest roentgenogram showed a centrally located, 12-cm mass in the right lower lobe (Fig 1). A computed tomographic scan of the chest also demonstrated several 1.0-cm to 1.5-cm paratracheal lymph nodes. At bronchoscopy we noted complete obstruction of the superior segment and the posterior-basilar segment of the right lower lobe. Biopsy specimens were diagnostic for a poorly differentiated carcinoma. Preoperative evaluation including laboratory studies, cardiac evaluation, and pulmonary function testing showed no contraindication to major pulmonary resection.

Mediastinoscopy and multiple lymph node biopsies were negative. At thoracotomy, no chest wall or mediastinal involvement was present. Manipulation of the lower lobe was difficult because of the size of the tumor. The pleura overlying the inferior pulmonary vein was thickened, but no tumor was appreciated within the vein. An extended pneumonectomy was performed including a portion of the left atrial wall with the inferior pulmonary vein. Margins were clear by frozen section.

On awakening, the patient complained of pain and partial paralysis in both lower extremities, which were cool and pulseless to examination. Bilateral femoral artery explorations were performed and a large aortic saddle embolus was removed, restoring forward flow to both legs. Frozen section of the embolus demonstrated tumor cells, which were confirmed on permanent sections (Fig 2). Approximately 6 hours later the patient had expressive aphasia and right hemiplegia. A head computed tomographic scan showed an ischemic left frontoparietal infarction consistent with an embolic event. A transesophageal echocardiogram was performed; no tumor or clot was seen within the left atrium.

The patient's neurological status slowly improved. His only subjective complaint was intermittent left leg pain with a normal vascular examination. A repeat computed tomographic scan of the head showed a resolving ischemic infarction. On the 12th postoperative day, he again complained of bilateral lower extremity pain and weakness. His examination was consistent with bilateral ischemia. A repeat exploration of both femoral arteries was promptly performed, and a second saddle embolus was removed from the aorta. Frozen and permanent sections of the embolus again demonstrated tumor cells.

The remainder of his hospitalization was uneventful. His neurological status slowly improved until his transfer to a rehabilitation unit. He thereupon completed an intensive neurological rehabilitation program without further improvement in his right hemiplegia or expressive aphasia. Since his discharge from the hospital, the patient has been unavailable to follow-up examination despite extensive but unsuccessful efforts to locate him. Therefore, his ultimate clinical outcome is not known.

All embolectomy specimens were confirmed pathologically as tumors of the same cell type as the primary pulmonary tumor, a poorly differentiated adenocarcinoma.

Comment

Microscopic evidence of angioinvasion in bronchogenic carcinoma is almost uniformly present if one examines for

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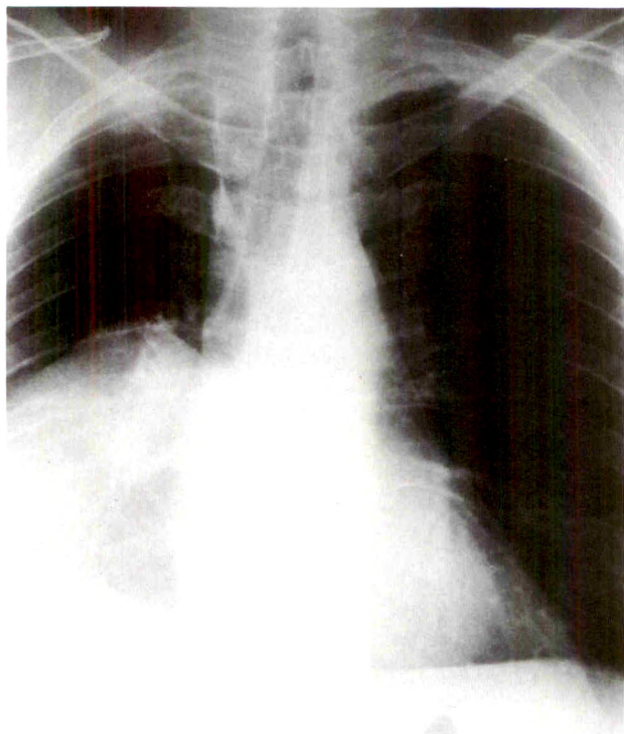


Fig 1. Posteroanterior preoperative chest roentgenogram showing centrally located 12-cm mass in the right lower lobe.

involvement in the tributaries of the pulmonary vein. However, the incidence of macroscopic pulmonary vein invasion by tumor is not well documented but may be up to 34% [3]. The importance of microscopic invasion in regard to long-term prognosis is questionable. The consequence of dislodging macroscopic tumor from the pulmo-

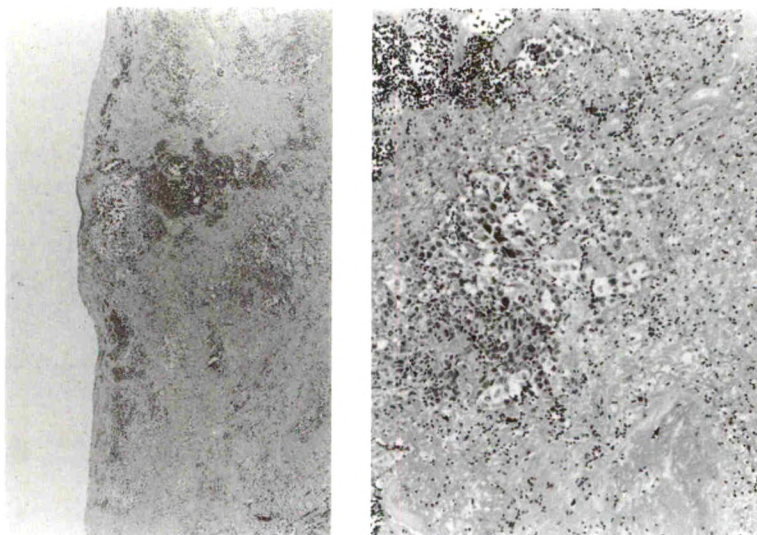
nary vein is often fatal [4]. Fortunately, surgical experience indicates that tumor extending into the proximal pulmonary veins or left atrium is rare and more likely to occur in bulky, centrally located tumors.

This patient had tumor extending into the proximal portion of the inferior pulmonary vein, which was not appreciated at exploration. The surgical manipulation in performing the extended pneumonectomy dislodged a portion of the tumor, resulting in the systemic emboli. The bulk of the tumor embolus lodged in the distal aorta and the aortic bifurcation, causing the lower extremity ischemia. The cerebral infarction presumably was the result of left middle cerebral artery embolization by a neoplastic mass, which was retained in the left atrium and dislodged in the immediate perioperative period. After two embolic events, a transesophageal echocardiogram was performed but showed no residual intraatrial mass. It is postulated that the second aortic saddle embolus, occurring 12 days after the first embolus and the negative transesophageal echocardiogram, resulted from a tumor embolus that initially lodged in the aorta proximal to the bifurcation.

To minimize the risk of tumor dislodgment during surgical manipulation, some authors recommend early ligation of the pulmonary veins. In patients with large central tumors who may be at increased risk for tumor dislodgment, early pulmonary vein ligation may be warranted. However, this procedure may be difficult or impossible to perform because of the size of the tumor.

In selected patients in whom an extended pneumonectomy is anticipated, consideration should be given to obtaining a preoperative transthoracic or transesophageal echocardiogram to evaluate for the presence of tumor within the pulmonary veins or left atrium; this examination can be performed before the thoracotomy. If tumor is

Fig 2. Tumor embolus. (Both stained with hematoxylin and eosin: left, $\times 100$; right, $\times 250$; both before 38% reduction.)



identified within the veins or atrium, modification of the surgical technique or the extent of resection will allow for a complete resection of tumor and possibly avoid the complication of systemic tumor emboli. Finally, tumor embolization, although uncommon, should be given consideration in the etiology of cerebral, extremity, or multiple organ ischemia that occurs in the perioperative period in patients undergoing pulmonary resection for malignancy.

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Preoperative Management of Neonatal Tetralogy of Fallot With Absent Pulmonary Valve Syndrome

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In tetralogy of Fallot with absent pulmonary valve syndrome, aneurysmal enlargement of the central pulmonary arteries can be associated with severe bronchial stenosis and respiratory distress in the neonatal period. The ventilatory status of these patients must be stabilized

before diagnostic and therapeutic interventions can be performed. This report describes the experience with prone positioning and emergency sternotomy in the preoperative care of a neonate.

(Ann Thorac Surg 1993;55:172-4)

Absent pulmonary valve syndrome accounts for 3% of all cases of tetralogy of Fallot. It consists of agenesis of the pulmonary valve with pulmonary insufficiency and annular pulmonary stenosis. The central pulmonary arteries are aneurysmally enlarged and may compress the tracheobronchial tree. The degree of this compression determines the clinical presentation. Severe obstruction can render the patient critically ill in the neonatal period. Respiratory failure may be predominant and necessitate emergency relief of the tracheobronchial compression.

A 3.6-kg male neonate was referred on the first day of life for evaluation and treatment of profound cyanosis and respiratory acidosis. At birth, endotracheal intubation and mechanical ventilation were necessary. However, respiratory function remained severely compromised during transfer to our institution. Echocardiography showed tetralogy of Fallot with absent pulmonary valve syndrome and massive central pulmonary artery aneurysms (diameter, 16 mm). Adequate ventilation could only be achieved with the infant in the prone position. In the supine position there was an instant increase in carbon dioxide tension and a decrease in oxygen tension (Table 1). He therefore underwent repair of his cardiac malformation.

During preparation for the surgical procedure the patient was repositioned on the operating table from the prone to the supine position for sternotomy. An immediate increase in the carbon dioxide level was noted, although the inspired oxygen fraction had been increased from 0.3 to 1.0. Emergency sternotomy was performed. Upon this, there was obvious immediate clinical improvement in his mechanical gas exchange, documented by consecutive blood gas analyses, before cardiopulmonary bypass was instituted (see Table 1).

Hypothermic circulatory arrest was established, and the

lesion was repaired. This included ventricular septal defect closure and aneurysmorrhaphy of the massively dilated main and branch pulmonary arteries, reducing them to normal size. In addition, a valved aortic homograft conduit (diameter, 9 mm) was implanted to reconstruct the right ventricular outflow tract, keeping its length short to lift the branch pulmonary arteries off the tracheobronchial structures.

Postoperatively there were stable hemodynamics and no carbon dioxide retention in the supine position as long as full ventilation was provided. However, attempts to wean the patient from the ventilator were unsuccessful for 2 weeks because of hypercapnia. Cardiac catheterization revealed relatively normal intracardiac hemodynamics with a right ventricular pressure about half systemic and no major shunts. There was residual distortion and dilation of the intraparenchymal lobar pulmonary arteries (Fig 1). Concomitant bronchography disclosed diffuse areas of narrowing in the secondary branches of the tracheobronchial tree, especially in the left lung (Fig 2). The patient was eventually extubated on the 31st postoperative day.

Since then the boy has suffered repeated upper respiratory tract infections, sometimes necessitating hospital treatment but never mechanical ventilation. There has been slow but constant improvement of his respiratory status, and he is now 2 years of age. No further operation has been necessary.

Comment

Tetralogy of Fallot with absent pulmonary valve syndrome may be seen in infancy with severe respiratory distress, caused by central airway compression by the enlarged pulmonary arteries. Early surgical correction including plasty of the pulmonary arteries has been advocated [1-5]. Mortality is still considerable owing to the poor clinical condition of the patients. An already decreased air exchange can be made even worse by additional intrapulmonary bronchial stenoses caused by abnormally branching peripheral pulmonary arteries [6].

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Table 1. Respiratory Status Data Varying With Positioning

Variable	Admission Day, ICU		Day of Operation			
	Supine	Prone	Before Sternotomy		After Sternotomy	
			Prone, OR	Supine, OR	10 Min	20 min
Pco ₂ (mm Hg)	60	34	40	69	57	35
Po ₂ (mm Hg)	22	56	67	68	149	358
pH	7.36	7.53	7.50	7.27	7.35	7.54
FiO ₂	0.3	0.3	0.3	1.0	1.0	1.0
Ventil	SIMV	SIMV	SIMV	CMV	CMV	CMV

CMV = continuous mandatory ventilation; FiO₂ = fraction of inspired oxygen; ICU = intensive care unit; OR = operating room; Pco₂ = partial pressure of carbon dioxide in arterial blood; Po₂ = partial pressure of oxygen in arterial blood; pH = acid-base status; SIMV = synchronized intermittent mandatory ventilation; ventil = mode of ventilation.

The airway obstruction should be relieved as completely as possible preoperatively, but intractable respiratory symptoms have been the main indication for emergency operation [1, 4, 5].

The preoperative clinical improvement of infants with symptomatic absent pulmonary valve syndrome in the prone position has been noted [7, 8]. This phenomenon is explained by the position of the enlarged pulmonary arteries, which fall posteriorly when the patient lies supine, thereby compressing the bronchi behind them.

A supine position is necessary for performing a median sternotomy. In the most severely compromised patients even short periods in this position may be tolerated poorly. In our case median sternotomy dramatically reversed this process (see Table 1). An awareness of this may prevent prebypass respiratory arrest in the operating room and also avoid "crashing" on bypass. One may speculate that in such patients, who also may require more prolonged resuscitation in the intensive care unit or

further diagnostic studies before operation is undertaken, an elective median sternotomy could be quite helpful in the overall management. This would allow the supine position to be tolerated for performance of various procedures, ranging from vascular access to cardiac catheterization. The wound can be sealed with a prosthetic patch.

Primary complete repair including ventricular septal defect closure, decompression of the airways by reduction plasty of the enlarged segments of the central pulmonary arteries, and valved homograft reconstruction of the main pulmonary artery is advocated by us for the treatment of symptomatic absent pulmonary valve syndrome in infancy. Additional intrapulmonary bronchovascular anomalies may contribute to severe respiratory problems after correction, as illustrated by our patient. It therefore seems appropriate to normalize the cardiovascular status as much as possible by complete repair including the placement of a pulmonary valve. Our philosophy is that any residual cardiac handicap, even one normally well toler-

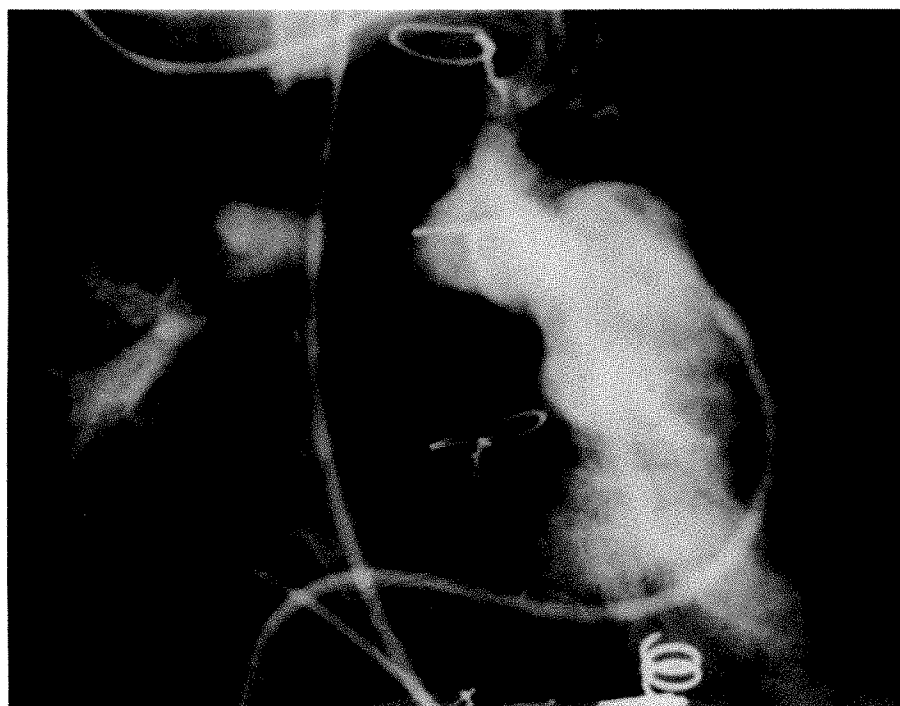
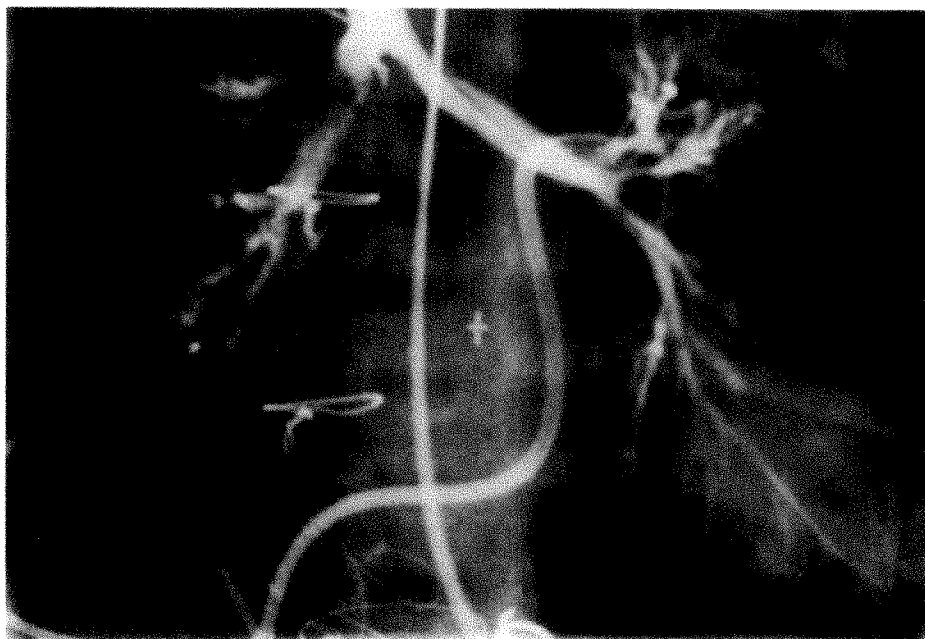


Fig 1. Cardiac catheterization on the 14th postoperative day: pulmonary arteriogram in anteroposterior position after reconstruction of the right ventricular outflow tract and the main pulmonary artery with a valved aortic homograft conduit, and after extensive reduction plasty of left and right pulmonary artery to diameters of about 5 mm. Distorted and still dilated proximal lobar pulmonary arteries can be seen. The regurgitation into the right ventricle is caused by the position of the catheter.

Fig 2. Bronchogram in anteroposterior position performed during the cardiac catheterization on postoperative day 14. Diffuse areas of narrowing can be seen in the secondary branches of the tracheobronchial tree: right middle and lower lobe, lingula, and especially left upper and lower lobe.



ated in standard tetralogy of Fallot, can have a devastating effect in the presence of inevitable long-term pulmonary disease.

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Retrograde Cardioplegia Cannulation During Cardiopulmonary Bypass

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A simplified method of transatrial cannulation of the coronary sinus during cardiopulmonary bypass, with the heart completely decompressed, is described. The technique is easy to adopt and inherently safe because the catheter is guided toward the great cardiac vein visually, rather than by manual palpation.

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Transatrial cannulation of the coronary sinus for the purpose of delivery of cardioplegia through the retrograde route has been efficacious in a variety of cardiac operations. The details of the technique as described by Gundry and associates [1] and Drinkwater and colleagues [2] involve placement of the retrograde cannula by manual palpation of the right atrioventricular groove to guide the catheter into the coronary sinus before establishment of cardiopulmonary bypass. Although facile in experienced hands, prolonged manipulation, which may occur, can result in hemodynamic instability and arrhythmias. Cannulation by palpation is also a partially blind technique, and misplacement of the catheter into a tributary of the coronary vein and even coronary sinus rupture are recognized complications that can occur.

We describe a technique that we have developed over the past year, which allows for rapid placement of the retrograde catheter after cardiopulmonary bypass is initiated. This technique is also different from that described in the recent communication by Arom and Emery [3] in that the catheter is positioned not by palpation, but by visually guiding it into the coronary sinus and the greater cardiac vein.

Technique

Cardiopulmonary bypass is initiated in standard fashion with aortic cannulation and a single venous cannula. The heart is completely decompressed. With the heart beating, the retrograde catheter is introduced into the right atrium through a small stab wound within a pursestring suture, which is then held up by the assistant to create an airtight seal. It is preferable to place the pursestring suture low in the right atrium.

From the surgeon's side, the heart is retracted cephalad with the left hand, visualizing the atrioventricular groove (Fig 1). With the right hand, the retrograde catheter with its tip gently curved (either by shaping the flexible stylet, or preferably by using a catheter with a preformed stylet) is guided and seen to engage the coronary sinus. At this juncture, it is a simple matter to then guide the tip of the catheter beyond the posterior interventricular vein by advancing the catheter itself without the stylet. Because the course of the great cardiac vein is visualized at all times, precise and safe placement is assured in every instance. We usually cannulate the coronary sinus shortly after cardiopulmonary bypass has been established, while the heart is still beating; however, this maneuver can be performed in the same way with the heart fibrillating.

The details are the same if one wishes to place the catheter from the assistant's side. The heart is retracted cephalad with the left hand, and the catheter is guided into the coronary sinus with the right hand. The visualization of the course of the great cardiac vein is equally good from this side, and therefore, the technique is equally facile and safe.

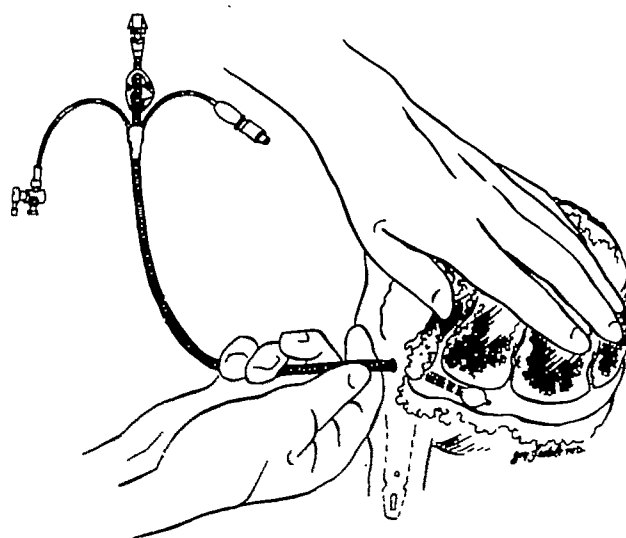


Fig 1. The heart is retracted cephalad from the surgeon's side with the left hand after cardiopulmonary bypass is initiated. The tip of the two-stage venous cannula is seen in the inferior vena cava. The great cardiac vein is visualized as the catheter engages the coronary sinus. The stylet is then withdrawn, and the tip of the catheter is guided distally.

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Comment

Early in our experience with retrograde cardioplegia, we initially adopted the technique described by Gundry and associates [1]. However, it became clear that there was a learning curve associated with this technique that inhibited more widespread acceptance. Also, the disadvantages of provoking hemodynamic instability while attempting to place the catheter before cardiopulmonary bypass and the small but finite risk of perforation of the coronary sinus with the technique of manual palpation became apparent.

Over the past year, the technique as described has been used as the sole method for transatrial cannulation of the coronary sinus in the 204 patients in whom this approach was indicated, including coronary bypass and mitral and aortic valve operations. We have used preferentially the Retroplegia cannula (Research Medical, Inc, Salt Lake City, UT) because we find the preformed stylet of this catheter to lend itself best to this technique. We have noted successful cannulation in all but 4 patients, with the average time being less than 10 seconds. In 4 patients, we

were unable to direct the catheter beyond the posterior interventricular vein although the catheter was seen to engage the coronary sinus. Presumably this was due to the presence of a flap or valve in the coronary sinus orifice. In these patients we administered cardioplegia antegradely and through the vein grafts. The incidence of iatrogenic injury to the coronary sinus has been nil. We present this technique as an added approach to the armamentarium of the surgeon in achieving safe myocardial protection.

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Simplified Method for Delivering Normothermic Blood Cardioplegia

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We describe a simple technique for optimizing oxygen delivery during normothermic continuous blood cardioplegia. It involves the use of a minimal volume of cardioplegic agents, the infusion rate of which is adjusted so as to keep the heart arrested. The resulting enhancement of oxygen supply is marshalled from the maintenance of hematocrit values in the range of 0.25.

(*Ann Thorac Surg* 1993;55:177-8)

Normothermic continuous blood cardioplegia is a recently described technique [1] that has yielded very encouraging results, in particular in patients at high operative risk because of impaired left ventricular function [2] or long cross-clamping time [3]. Until now, normothermic continuous blood cardioplegia has been used in the same manner as cold blood cardioplegia, that is, blood is diluted with crystalloid cardioplegic solution in a 4:1 ratio. In practice, the technique requires two cardioplegic solutions, one (high K^+) for inducing and the other (low K^+) for maintaining arrest, with an eventual switch back-and-forth between the two perfusates if there is recurrence of cardiac activity during the cross-clamping period. The whole cardioplegia delivery set-up is rather complex and costly. Assuming that it was probably not the most appropriate under *normothermic* conditions, we have designed a simple, effective, and inexpensive delivery technique of normothermic continuous blood cardioplegia, which is described further herein.

Technique

Standard perfusion tubing (0.63 cm [2.5 inches] in diameter) is connected at one end to the top of the oxygenator and at the other end to the cardioplegia infusion catheter (Fig 1). This tubing passes through a separate roller pump, which allows delivery of cardioplegia at a controlled flow rate. The distal limb of the tubing (that is, the segment between the pump and the patient) incorporates a three-way stopcock, which is used for the delivery of our "mini" cardioplegic solution. Namely, this solution is made of 20 mL ampoules that contain only potassium

chloride (16 mEq per ampoule) and magnesium chloride (6 mEq per ampoule) in distilled water.

As soon as the ascending aorta has been cross-clamped, blood perfusion is initiated through the aortic root at a flow rate of 300 mL/min. Simultaneously, the full content of one ampoule is manually injected over approximately 30 seconds through the side port of the three-way stopcock. Cardiac arrest is achieved within 1 minute of aortic cross-clamping. As soon as the heart is arrested, the cardioplegia line is switched to a retrograde coronary sinus catheter and the flow rate of the pump is reduced to approximately 150 to 200 mL/min. An electrically driven syringe (Vial Medical, Grenoble, France) is then connected to the stopcock and allows the continuous delivery of cardioplegia during the remainder of the cross-clamping period. This syringe is filled with three of our cardioplegic ampoules, which represents a total volume of 60 mL. The rate of infusion is initially set at 45 mL/h because we have found that, on the average, this value allows us to keep the heart arrested. When there is a recurrence of electromechanical activity, the flow rate of the cardioplegia delivery syringe is transiently increased until activity ceases (we have gone up to 60 mL/h), except when the pattern of cardiac activity features "creeping" waves rather than rhythmic contractions, in which case a bolus of procaine (5 mL of a 1% solution) is more effective than an increase in potassium load. Once the heart is arrested again, the infusion rate is gradually brought back to its initial value. Whenever a stable asystole seems to have been achieved, attempts are made to progressively reduce the rate of infusion below the average value of 45 mL/h, and it is not uncommon that beyond approximately 30 minutes of aortic cross-clamping, an infusion rate in the range of 30 mL/h is effective in maintaining cardiac arrest (just as if an initially effective "impregnation" of the myocardium by the potassium-magnesium mixture allowed a reduction in the amount of cardioplegic agents subsequently required for maintaining cell depolarization).

Thus, for a 2-hour period of aortic occlusion, the volume of crystalloid cardioplegia delivered would be typically 65 mL (20 mL for induction and 45 mL for maintenance), which represents a total potassium load of 52 mEq (in fact, this load will often be less because, as previously stated, the infusion rate is itself frequently less than 45 mL/h during the last part of the procedure). Until now, hyperkalemia at the end of bypass has not been a clinical

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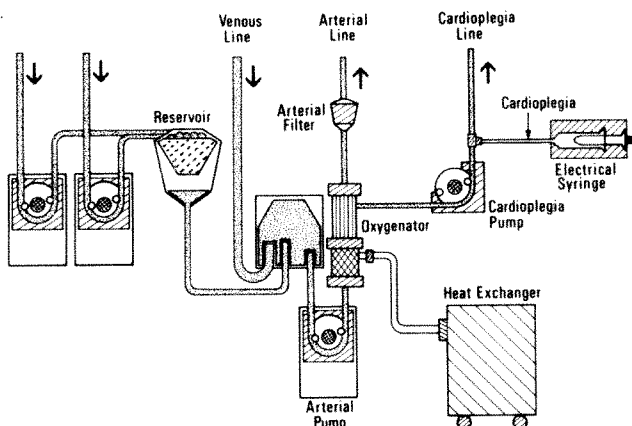


Fig 1. Cardioplegia set-up.

cally relevant problem. Furosemide is only used when the urine output is inadequate.

Comment

Normothermic continuous blood cardioplegia is based on the observation that electromechanical work is the main determinant of myocardial oxygen requirements [1]. Consequently, the chemically induced abolishment of electromechanical activity, without added hypothermia, is expected to reduce metabolic needs to such an extent that they can be adequately matched by the continuous delivery of normothermic blood.

Because these residual metabolic needs cannot be predicted accurately in a given heart (and, in fact, most likely vary from one heart to another), it sounds logical to supply as much oxygen as possible to prevent the occurrence of an energy deficit and a subsequent anaerobic metabolism during arrest. In practice, optimization of oxygen supply can be achieved by maintaining a high flow rate of cardioplegia delivery (at least 150 mL/min when retroperfusion is used) together with a high oxygen content in the cardioplegic blood. The latter objective implies, in turn, that one should not dilute further blood that is already diluted by the pump prime, hence our concern about delivering a minimal volume of crystalloid cardioplegia by making up the cardioplegic "solution" with the sole additives that are likely to be critical in normothermic continuous blood cardioplegia, that is, the arresting agents.

The usefulness of the other usual components of cardioplegic solutions can be questioned in the setting of continuous perfusion with normothermic blood. Assuming that the preferred substrates of the heart are free fatty acids, glucose, and lactate [4], amino acid supplementation becomes debatable. Likewise, it is doubtful that artificial buffers (like tromethamine) or osmotic agents

provide protection beyond that due to the buffering and protein-based oncotic capacities of blood. A more important concern is the prevention of calcium overload, which can be enhanced by potassium-induced membrane depolarization [5]. To address this issue, we have used the natural calcium antagonist magnesium rather than the commonly used citrate-phosphate-dextrose chelating solution because magnesium could more effectively contribute to sustained asystole [5]. Limitation of the cardioplegic formulation to potassium and magnesium allows us to concentrate these ions in a small volume and, consequently, to virtually eliminate cardioplegia-induced hemodilution.

This technique has four attractive features: (1) It is simple. Perfusionists become rapidly familiar with the way of "playing" with the knob of the electrical syringe so that delivery of the smallest dose of cardioplegia can be conciliated with maintenance of arrest. From this standpoint, it seems at least as easy to handle a single cardioplegic formulation, the infusion rate of which is adjusted on-line, as to deliver alternatively two solutions differing by their potassium content. (2) It is effective in optimizing oxygen delivery as reflected by hematocrit values averaging usually 0.25, which has been shown to correlate with optimal preservation of normothermically perfused human hearts [6]. (3) It is inexpensive because apart from cardioplegia cannulas, the disposable delivery system only includes a single piece of tubing, a stopcock, and cardioplegia ampoules of simple formulation and, consequently, of low cost. (4) It is flexible as far as the temperature of the blood cardioplegic infusate is concerned because a separate heat exchanger can be easily incorporated in the cardioplegic circuit, thereby allowing one to meet an unexpected requirement for rapid cooling.

We acknowledge the active contribution of our perfusionists, Mrs Emmanuelle Baconnet, Maggy Devaux, Dominique Ponthier, and Mr Alain Bloquaux.

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Autologous Pericardial Flap for Prevention of Reentry Injury in Cardiac Reoperations

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Cardiac injury during sternal reentry to the heart is a rare but dangerous complication of cardiac reoperations. Positioning a pericardial flap between the heart and sternum at the time of the initial operation may consistently facilitate cardiac reoperation by providing a reliable plane of dissection and by reducing adhesion formation.
(*Ann Thorac Surg* 1993;55:179-80)

Epicardial and mediastinal adhesions are a reoperative challenge and can lead to serious problems, such as cardiac damage, catastrophic hemorrhage, and increased dissection time. To minimize the risk of complications during sternal reentry, the use of pericardial substitutes has been advocated [1-3]. However, in a recent survey 14% of surgeons reported that they were dissatisfied with these substitutes at reoperation [4]. A pericardial flap, the interposition of a pedicle of pericardium between the heart and sternum, has been shown to be a safe, simple, and effective means of preventing mediastinitis and sternal dehiscence after cardiac operations [5]. Since adopting the routine use of the pericardial flap technique in 1986, we have performed 13 reoperations in patients who had pericardial flap coverage during the primary cardiac operation. This report describes our experience with these operations and discusses the use of an autologous pericardial flap and its protective role during sternal reentry at the future cardiac reoperation. Our technique and results are described.

Technique

The pericardial flap technique used by us has been previously reported [5]. After a median sternotomy incision, the left pleural space is opened widely and, in most cases, the internal thoracic artery is harvested. The pericardium is opened at its junction with the diaphragm. The incision is made to the pleuropericardial reflection on the right, parallel to the diaphragm, and toward the ventricular apex on the left. The incision is then directed cephalad just lateral to, and following the course of, the left anterior descending artery to the level of the pulmonary artery. The pericardium and remaining mediastinal fat and thymic tissue are then divided as the incision courses ob-

liquely over the pulmonary artery to the aorta and along the inferior border of the innominate vein (Fig 1). The flap may be affixed to the right side of the sternal retractor by stay sutures or folded into the right chest while the operation progresses. If stay sutures are used along the left pericardial edge, care must be taken to avoid injury to the phrenic nerve.

Upon completion of the cardiac operation, separate mediastinal drainage catheters are placed in the posterior pericardial and left pleural spaces. Before the sternum is closed, the pericardial flap is placed over the right ventricle to ensure the presence of pericardial tissue between the heart and sternum. In the cases of myocardial revascularization, no effort was made to cover the left internal thoracic artery graft to the left anterior descending artery. To minimize the risk of pericardial tamponade and to promote the mediastinal drainage into the left pleural space, the pericardial flap was not sewn to any adjacent structures. After a successful resternotomy, the pericardial flap may be dissected from the undersurface of the left side of the sternum until the edge of the flap is

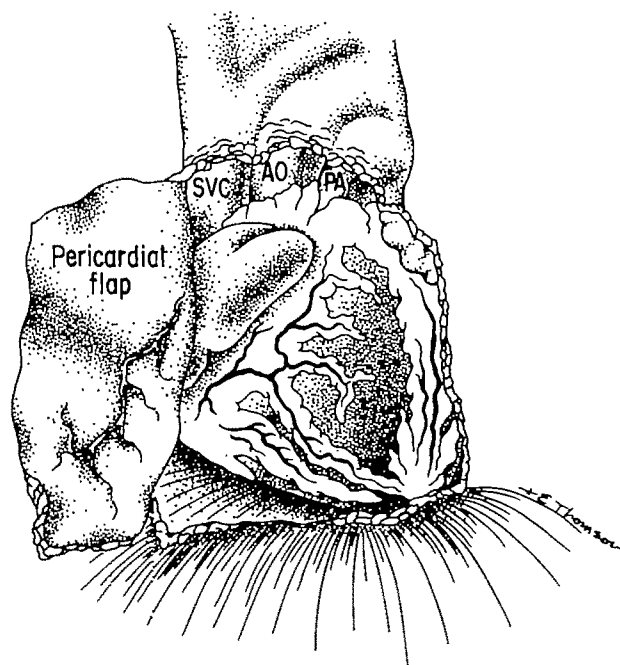


Fig 1. A prepared pericardial flap and its relationship to the other structures. (AO = aorta; PA = pulmonary artery; SVC = superior vena cava.)

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identified and elevated off the epicardium. Appropriate operation may then be performed in the usual manner. The flap may also be reused at the completion of the reoperation if a future cardiac reoperation is anticipated.

Comment

We have performed cardiac reoperations in 13 patients who had undergone a primary cardiac operation with the use of a pericardial flap. Primary and repeat operations included coronary artery bypass grafting in 7 patients, aortic valve replacement in 4 patients, and mitral valve replacement in 2 patients. In all 7 patients having coronary artery bypass grafting, the left internal thoracic artery had been used as a graft to the left anterior descending artery during the primary cardiac operation. At reoperation, sternal reentry was established within a few minutes in all patients. Catastrophic hemorrhage and damage to the cardiac structures have not occurred in any of these patients. Epicardial and mediastinal adhesions were easy to dissect and were associated with decreased dissection time.

In summary, the routine use of a pericardial flap may consistently facilitate a cardiac reoperation. Fast and safe sternal reentry may reduce the operative time and may eliminate the risk of iatrogenic injury during resternotomy.

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Use of Expanded Polytetrafluoroethylene Pericardial Substitute With Ventricular Assist Devices

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Expanded polytetrafluoroethylene membrane was used to reconstruct the pericardium after ventricular assist device insertion in 7 consecutive patients. One patient remains on support with the membrane in place and 6 have had the membrane removed. The expanded polytetrafluoroethylene membrane protected the device can-

nulas during repeat sternotomy and expedited the dissection of the heart and great vessels at the time of device removal. Reconstruction of the pericardium with expanded polytetrafluoroethylene membrane is recommended at the time of ventricular assist device insertion.

(*Ann Thorac Surg* 1993;55:181-3)

Ventricular assist devices (VADs) are currently used to support the circulation of critically ill patients until a donor heart becomes available or cardiac recovery occurs. We have noted that mediastinal adhesions become progressively more severe during the first several weeks after VAD insertion and prolong the dissection necessary when the VAD is removed. Expanded polytetrafluoroethylene (e-PTFE) pericardial substitute is recommended to minimize these adhesions and facilitate subsequent transplantation.

Technique

After completing VAD insertion a sheet of 0.1-mm e-PTFE membrane (Gore-Tex Surgical Membrane; W. L. Gore and Associates, Inc, Flagstaff, AZ) is placed between the pericardium and the epicardium laterally and between the VAD cannulas and overlying sternum anteriorly (Fig 1). The e-PTFE sheet is first placed between the right atrium and the pericardium, and the remaining portions of the membrane are tucked between the lateral and inferior surfaces of the ventricles and the pericardium. Mediastinal drainage tubes are left above and below the membrane, and interrupted monofilament sutures are used to secure the pericardial edges to the membrane. The VAD cannulas themselves are not wrapped with e-PTFE membrane. The sheet of e-PTFE should be placed over the heart in a position that minimizes creases and folds; however, no attempt is made to produce a watertight seal around the heart.

When the chest is reopened, the edge of the e-PTFE membrane is palpated immediately below the xiphoid process, and the plane between the membrane and the sternum is established. An oscillating saw is used to

divide the sternum, and the sternal fragments are dissected from the e-PTFE surface (Fig 2). The e-PTFE membrane is then lifted from the surface of the heart.

Results

Expanded polytetrafluoroethylene pericardial substitute has been used in 7 consecutive patients who required VAD support pending cardiac transplantation. As of July 30, 1992, one patient remained on support with the membrane in place. In the other 6 patients, the membrane was removed after a mean of 143 ± 39 days (range, 35 to 279 days). At re sternotomy, the e-PTFE membrane protected Dacron grafts to great vessels and the right ventricle from injury. The plane of dissection between the heart and the pericardium was visible after removal of the intact e-PTFE sheet (Fig 3).

Infection of the e-PTFE membrane occurred in 2 patients. Membrane infections developed in both of these patients after a second sternotomy, and both infected membranes cultured *Staphylococcus aureus*. In the first patient, a second sternotomy was required for relief of delayed tamponade. The e-PTFE membrane was removed 35 days later when fever and leukocytosis developed. This patient is currently well and is awaiting transplantation. In the second patient, the e-PTFE membrane became infected after a second sternotomy for transplantation. The transplant procedure was aborted due to acute procurement failure of the donor heart, and the e-PTFE membrane was left in place. This mediastinal infection remained indolent and was not confirmed until shortly before the patient's death. There were no other membrane-related complications.

Comment

Insertion of a VAD as a bridge to cardiac transplantation commits the patient to a second sternotomy. Donor avail-

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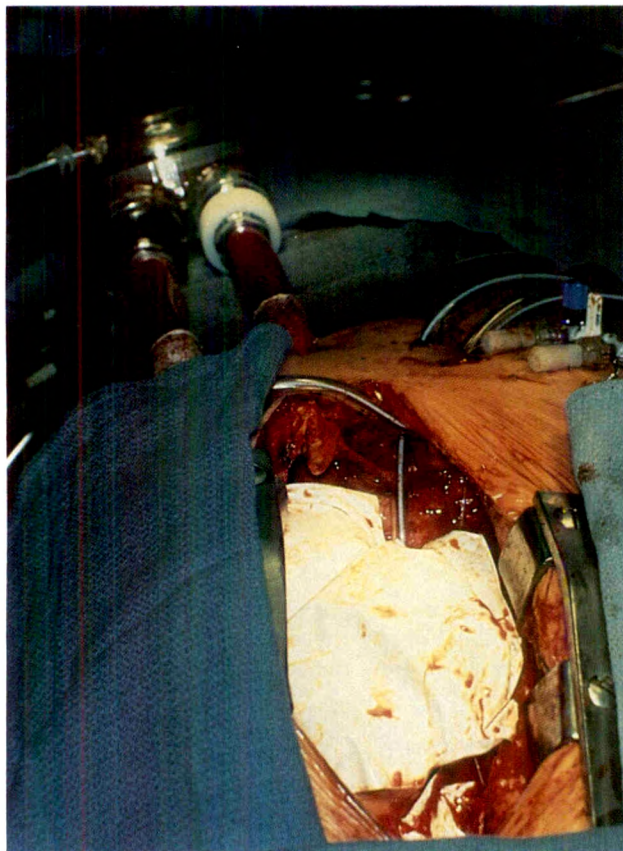


Fig 1. In this view from the patient's head, the expanded polytetrafluoroethylene membrane is seen in place over the heart and cannulas for a left ventricular assist device.

ability is uncertain, and in our recent experience waiting periods of several months are common. Adhesions that form during the waiting period can prolong the transplantation procedure and increase blood loss, particularly if the patient is maintained on therapeutic levels of anticoagulation. Dense adhesions between the graft(s) and overlying sternum pose a special risk for serious hemorrhage at reoperation. Thus, the use of a pericardial substitute seems worthwhile.

Investigators at the University of Utah have suggested using glutaraldehyde-fixed pericardium to facilitate reoperation after implantation of a total artificial heart [1]. However, reports of dissatisfaction with bovine pericardial substitute in humans [2] persuaded us that e-PTFE membrane would be a better choice. Studies in animals [3], as well as experience with e-PTFE membrane in humans [2, 4], have shown that fibrous adhesions to the e-PTFE membrane are mild and calcification does not occur. Epicardial thickening occurs in reaction to the e-PTFE membrane and can obscure coronary anatomy, but this is of little importance before transplantation. Our own clinical experience supports the use of the e-PTFE membrane at the time of VAD implantation to increase the safety of reoperation and the ease of subsequent dissection at the time of transplantation.

There is a risk of infection when any foreign material is

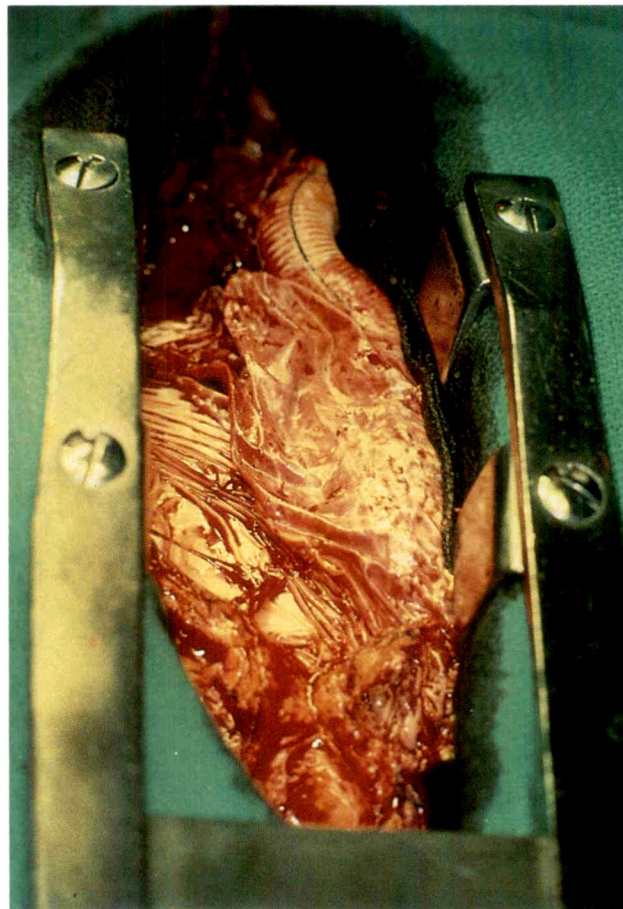


Fig 2. At resternotomy for cardiac transplantation, the expanded polytetrafluoroethylene membrane protects the right ventricle and Dacron conduits from injury. The expanded polytetrafluoroethylene membrane also facilitates dissection of the heart from the pericardium.

left in the body. The incidence of infection for e-PTFE membrane used to reconstruct the pericardium after other cardiac operations is low [2, 4], whereas the incidence of infection related to VAD use is higher [5]. It is possible

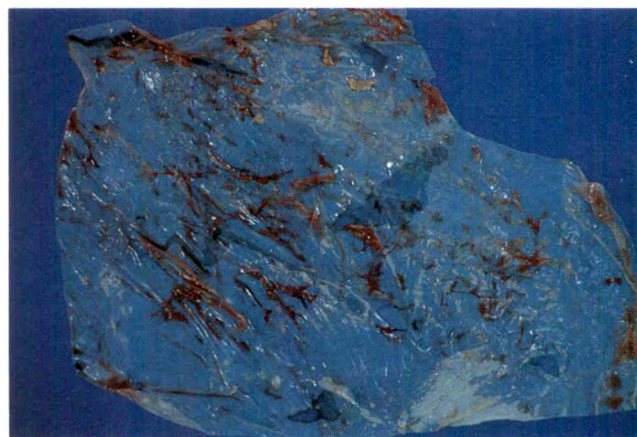


Fig 3. Expanded polytetrafluoroethylene membranes that are in place for several weeks become translucent but retain structural integrity and can be removed intact from the mediastinum at the time of transplantation.

that the presence of an e-PTFE membrane increases the risk for mediastinal infection after VAD insertion. However, note that in the 7 patients of this study e-PTFE membrane infections only occurred after a second operation, and one of these two infections was successfully managed by removal of the membrane with antibiotic therapy. Clearly, meticulous sterile technique is essential when a VAD or an e-PTFE membrane is placed in the chest, and continued monitoring of infectious complications in these patients is indicated. If signs of infection occur, membrane- or VAD-related infections must be suspected and aggressively treated.

This work was performed during Dr Holman's tenure as an Established Investigator for the American Heart Association.

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Naming the Bronchopulmonary Segments and the Development of Pulmonary Surgery

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An international agreement on bronchial nomenclature and anatomy was not reached until well after operations for bronchopulmonary segmental disease were well developed. R. C. Brock, in 1950, was the reporter of the efforts of The Thoracic Society of Great Britain to bring some order to this confused state. This Society delayed its action until an ad hoc committee made up of members from other countries and specialties met at the International Congress of Otorhinolaryngology in 1949. The

anatomy and nomenclature of the bronchopulmonary segments was agreed upon. The Thoracic Society then accepted the report of the ad hoc committee. The system was followed closely by the first *Nomina Anatomica* in 1955. This report did not open new surgical vistas but was the marker indicating that pulmonary surgery was now mature.

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By the mid-1900s the practice of excisional pulmonary surgery had become progressively more selective in preserving pulmonary tissue by substituting lobectomy for pneumonectomy in many malignancies and segmentectomy for lobectomy in infections and other segmental diseases. In spite of this remarkable progress, the anatomy and the nomenclature of the bronchopulmonary segments were not clearly established. In 1949, The Thoracic Society of Great Britain recognized this problem and initiated a move that led to the significant report by Russell C. Brock, "The Nomenclature of Bronchopulmonary Anatomy: An International Nomenclature Accepted by The Thoracic Society" [1]. This recommendation became widely accepted and was only slightly modified in the *Nomina Anatomica* in 1955 and the years following. This consensus statement did not suddenly open new vistas to the thoracic surgeon, but was, in fact, an indicator that lung surgery had reached its zenith and was based on sound anatomic facts.

In the first quarter of the century, anatomic atlases, texts, and descriptions of the segmental bronchi were not portrayed in any detail. For example, *Morris's Human Anatomy* [2] and Werner Spalteholz's *Hand Atlas of Human Anatomy, 7th Edition* [3], showed excellent metal casts of the bronchial tree but contained no accompanying segmental detail. *Eparterial* was the descriptive term for the right upper lobe because of its course above the pulmonary artery. *Hyperarterial* was the term used for the middle and lower bronchi. The segments were described as arising alternately anteriorly and posteriorly, from the bronchus. These designations stemmed from Aebey's work, a study in comparative anatomy, which has been summarized by Huntington [4] and Boyden [5].

The concept of a defined segment of lung leading into a

specific bronchial branch was originated by Ewart [6], a pathologist at the Brompton Hospital in London. He described the bronchi as being distributed to specific pulmonary districts. In 1932, two American nose and throat surgeons, Rudolph Kramer and Arael Glass [7] of New York, agreed with this concept but suggested the term *bronchopulmonary segment* be assigned to the districts. They proposed a system of nomenclature, noted the relationship of the lung segments to the chest cage as shown on x-ray films, and suggested how this information might be used in treating lung abscesses.

The confused state of the nomenclature together with the anatomy of the bronchopulmonary segments in the years just before Brock's report are illustrated by a publication in 1942, "War Injuries of the Chest" [8]. This was edited by H. Morriston Davies and Robert Coope and was intended for use by the military and civilian casualty surgeons in Great Britain (Fig 1). Note that an axillary segment is represented by a circular opening in the upper lobe bronchus. This was often considered to be a separate segment that extended directly to the axilla and was thus viewed end-on in the lateral x-ray films. It is, in fact, the right upper lobe bronchus. The axillary portions of the upper lobes are normally supplied by two subsegments as shown in Figure 2. Also note that on the left, a middle lobe seems to arise from the left main bronchus. Among other reports in the English language, with variations in nomenclature and anatomy, are those of Adams and Davenport [9], Nelson [10, 11], Neil, Gilmour, and Gwynne [12], Appleton [13], and Foster-Carter [14]. Many of these studies illustrated their observations with bronchograms.

Two reports appeared in the early 1940s that had a profound impact on the establishment of the nomenclature and descriptions of segmental bronchopulmonary anatomy. The first originated in the United States, the second from Great Britain. Bronchoesophagology became a well-developed subspecialty of otorhinolaryngology in

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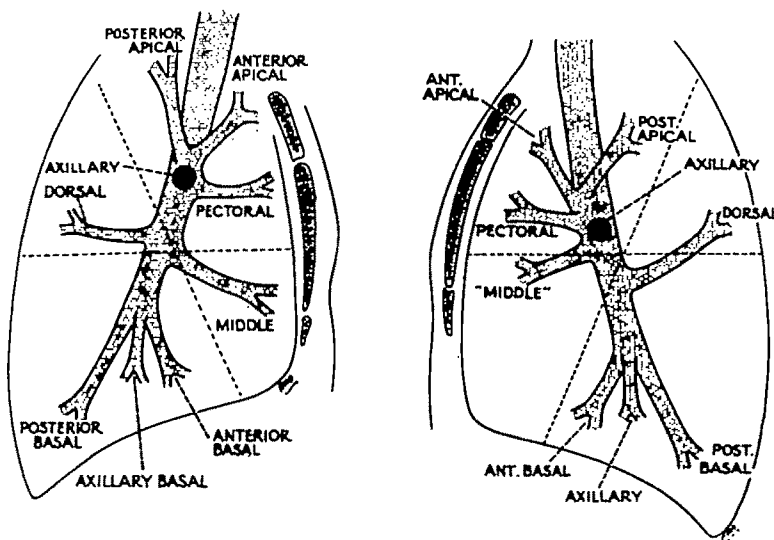


Fig 1. The segmental bronchi shown in the lateral projection, right number 4, left number 5. This appeared in "War Injuries of the Chest" published in Great Britain in 1942. Note that there are additional segments (axillary) shown in the upper lobes. The axillary bronchus was thought to extend in a straight lateral direction to the axillary area. This is, in fact, the right upper lobe orifice. The lingula appears to arise from the left main bronchus and is called the middle lobe. No medial basal segment is shown on the right or left. The exact origin of the nomenclature is not given. (Reprinted from Davies HM, Coope R, eds. War injuries of the chest, Edinburgh, E & S Livingstone, 1942:4, 5, with permission.)

the first half of this century, and its practitioners were concerned with the identification of segmental bronchial orifices and their relationship to the appropriate lung segments and their projection on x-ray films. Chevalier L. Jackson, a bronchoesophagologist, and John F. Huber, an anatomist, both of Philadelphia, accurately described the anatomy and proposed a simple system of nomenclature for the bronchopulmonary segments. This was published

in *Diseases of the Chest* in 1943 [15]. Their system of nomenclature is still closely followed by the *Nomina Anatomica* (Table 1). This was the only report of their work other than a paper by Huber in 1949 [17]. Jackson and Huber [15] explained the need for their studies by the following: "In any event we feel that the time has come when every bronchoscopist, certainly every bronchologist, must think in terms not of lobar bronchi or of lobes, but also segmental bronchi and broncho-pulmonary segments . . ."

In an effort to obtain precise information concerning the bronchopulmonary segments, which could be applied to the surgical treatment of lung abscesses and other lung infections, Russell C. Brock in England carried out extensive dissections with elegant reconstructions of the bronchopulmonary segments, lobes, and lungs. He related the findings to chest roentgenograms and bronchograms. He first published his observations in a series of articles in *Guy's Hospital Reports* starting in 1942, and then com-

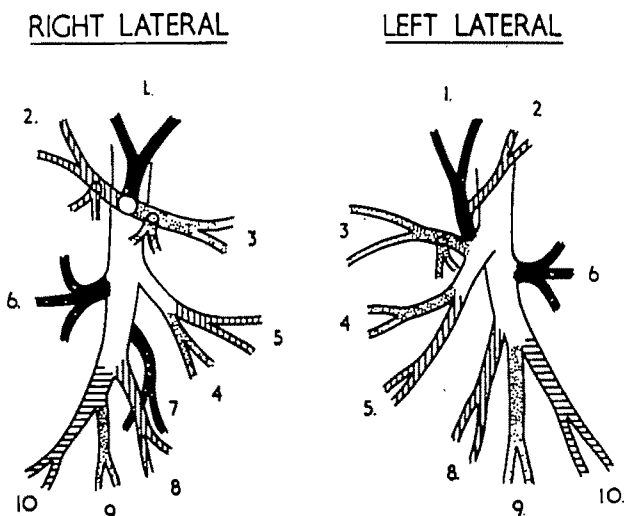


Fig 2. The anatomy and recommended nomenclature of the segmental bronchi proposed by the International Committee in 1949. The numbers refer to the names listed in Table 2. Note that a medial basal segment, number 7, is not shown on the left. The subsegments in the upper lobes shown on the right anterior and posterior segments and the left anterior segment are distributed to the axillary area. Singling out these subsegments may have been due to the fact that many believed that there was a separate segmental bronchus to the axillary area. The question of the name of the right bronchus between the upper and middle lobes was settled by calling it the lower part of the right main bronchus instead of bronchus intermedius. (Reprinted from Brock RC. The nomenclature of broncho-pulmonary anatomy: an international nomenclature accepted by The Thoracic Society. *Thorax* 1950;5:224, with permission.)

Table 1. 1969 *Nomina Anatomica* Nomenclature^a

Right	Left
Right upper lobe bronchus	Left upper lobe bronchus
I Apical	I, II Apico-posterior
II Posterior	
III Anterior	III Anterior
Middle lobe bronchus	
IV Lateral	IV Superior lingula
V Medial	V Inferior lingula
Right lower lobe bronchus	Left lower lobe bronchus
VI Superior	VI Superior
VII Medial basal (cardiac)	VII Medial basal (cardiac)
VIII Anterior basal	VIII Anterior basal
IX Lateral basal	IX Lateral basal
X Posterior basal	X Posterior basal

^a The 1989 *Nomina Anatomica* nomenclature [16] of the bronchial tree is now like that of Jackson and Huber except for separating antero-medial into anterior and medial to denote two of the basal segments.

bined the studies in a monograph published in 1950 entitled "The Anatomy of the Bronchial Tree With Special Reference to Surgery of Lung Abscesses" [18]. A second edition [19] appeared in 1954 in which the ad hoc International Committees' nomenclature was used. These studies became the models of surgical anatomic research. The senior author was fortunate enough to have seen the superb models used to illustrate Brock's papers at the Brompton Hospital in 1944.

In 1945, Edward A. Boyden [20], a member of the Department of Anatomy at the University of Minnesota, first became aware of the problem facing the surgeon in performing segmental resections. He described this as follows: "This article is an outgrowth of a surgical staff conference in which the author was asked by Dr. Owen H. Wangenstein to discuss the anatomy of the segmental pneumonectomy. Search of the literature having failed to yield any comprehensive figures of dissection of the external and the interlobar surfaces of the lung, the author was obliged to make preliminary dissections. The present article is an attempt to remedy that defect in the literature." Boyden [5] adapted the nomenclature of the bronchi proposed by Jackson and Huber, and included extensive dissections of the vascular supply of the lobes and segments, using a numbering system for all the elements. His work showed the relationship of the vascular anatomy with the bronchial anatomy, thus completing the map the surgeon needed for segmental resections.

Well before Brock's report on the nomenclature of the bronchopulmonary segments, surgeons were developing procedures for their removal. Edwin Churchill and Ronald Belsey [21], in 1939, reported their method for lingular and basal segmental resections for bronchiectases, and thus emerged the concept of segmental resection as a means of preserving functioning pulmonary tissue. A report by Brian Blades [22] on removing basal segments appeared in 1943. In 1947, Richard Overholt and Lazaro Langer published a significant article, "A New Technique for Pulmonary Segmental Resection. Its Application in the Treatment of Bronchiectasis" [23]. Details were given on the treatment of 21 patients. The segments removed were the lingula and the basal segments and the anterior segment of the right upper lobe. The authors stressed the use of blunt dissection. In 1947 Gordon Scannell [24] reported his experience with resection of the medial basal segment of the lower lobe of the right and the anterior segment of the left upper lobe. He continued his work in the laboratory with Boyden on segmental anatomy [25, 26]. Beatty Ramsay, in 1949, described the importance of the segmental veins as guides to the intersegmental plane [27].

The need for a clear definition of the anatomy and an accepted system of nomenclature was now critical, for surgery for segmental disease was well established. To remedy this problem, at least in Great Britain, The Thoracic Society in May of 1949 formed a committee made up of R. C. Brock (a surgeon), A. F. Foster-Carter (a physician), A. B. Appleton (an anatomist), and V. E. Negus (a nose and throat surgeon) [1]. Just before the committee completed its report, it learned that Professor E. Huizinga of the Netherlands had requested that an ad hoc interna-

tional group be formed to consider this same problem at the forthcoming International Congress of Otorhinolaryngology meeting in July 1949 in London. The Thoracic Society therefore tabled their study, believing that action by this group would more likely lead to the worldwide acceptance of the system.

The International Committee was composed of 15 members. Among them were Brock, Negus, Appleton, and T. Nicol of The Thoracic Society of Great Britain and four bronchoesophagologists, Chevalier L. Jackson, Paul Holinger, Louis Clerf, and Gabriel Tucker, the only members from the United States. This representative committee agreed that the system adopted should be simple and easily translatable into different languages, and that it should conform to established knowledge and descriptions of anatomy. Each bronchopulmonary segment would receive a number. The part of the lungs supplied by the segmental bronchus would be given the name of the segmental bronchus.

The committee considered five systems of anatomy and nomenclature [1]. These were submitted by Brock, Foster-Carter, Jackson and Huber, Huizinga, and Kourisky, the latter being from France. The greatest problem was nomenclature, for the anatomic descriptions in the five systems differed in only a few minor details (Table 2). However, there was disagreement about the status of the medial basal segment on the left as a separate segment. Jackson and Huber combined the medial and the anterior basal segments, naming them the anterior-medial basal segment, and noted that they arose from a single branch of the lower lobe bronchus. One question posed was whether apical, used by Brock, or superior, used by Jackson and Huber, would designate the first segment of the lower lobe. Apical was accepted at the expense of superior. Brock's middle basal segment was changed to lateral basal segment. Figure 2 shows the anatomy of the bronchial tree agreed upon. The conclusions of the International Committee were accepted by The Thoracic Society. R. C. Brock recorded this event in *Thorax* in 1950 [1]. This international accord resolved the major disagreements in bronchopulmonary segmental anatomy and presented a reasonable system of nomenclature that served until the publication of the first *Nomina Anatomica* in 1955 [28]. The latter followed The Thoracic Society's report very closely, using apical for superior to designate the first segment of the lower lobe, and including the subapical segment of the lower lobe as described by Brock. The latter was in parentheses, designating it as acceptable but not recommended. In the recent *Nomina Anatomica* [16] superior has replaced apical, subapical has been deleted, and medial basal segment is included (see Table 1).

The series of events defining the anatomy and leading to a widely acceptable nomenclature of the bronchopulmonary segments confirms the over-used expression: "Necessity is the mother of invention." This orderly progression, delineating the precise anatomy of the bronchopulmonary segments, began with the bronchoscopist's need to know where the segmental bronchi originating from the orifices, noted in the bronchoscope, were distributed. The surgeon needed to be able to determine

Table 2. The Nomenclature Adopted by the Ad Hoc International Committee Meeting at the Time of the International Congress of Otorhinolaryngology in 1949 [1]*

International Nomenclature	Brock	Jackson and Huber
Right upper lobe bronchus		
Apical (1)	Pectoral	Anterior
Posterior (2)	Subapical	Posterior
Anterior (3)	Apical	Apical
Middle lobe bronchus		
Lateral (4)	Lateral	Lateral
Medial (5)	Medial	Medial
Right lower lobe bronchus		
Apical (6)	Apical	Superior
Medial basal (cardiac) (7)	Cardiac	Medial basal
Anterior basal (8)	Anterior basal	Anterior basal
Lateral basal (9)	Middle basal	Lateral basal
Posterior basal (10)	Posterior basal	Posterior basal
Left upper lobe bronchus		
Upper division	Apicopectoral	Upper division
Apical (1)	Apical	Apical
Apicoposterior 1 and 2	...	Apical-posterior
Posterior (2)	Subapical	Posterior
Anterior (3)	Pectoral	Anterior
Lingula	Lingula	Lower (lingular) division
Superior (4)	Upper	Superior
Inferior (5)	Lower	Inferior
Left lower lobe bronchus		
Apical (6)	Apical	Superior
Anterior basal (8)	Anterior basal	Anterior medial basal
Lateral basal (9)	Middle basal	Lateral basal
Posterior basal (10)	Posterior basal	Posterior basal

* Two of the five systems, those of Brock and Jackson and Huber, are included. The problem of the presence of a medial basal segment on the left was not resolved and omitted entirely. Brock's apical instead of Jackson's and Huber's superior was adopted for the first branch of the lower lobe.

the precise location of lung abscesses and other inflammatory disorders for successful treatment. The importance of confining resections just to the diseased part of the lobe became paramount as indications for lung surgery broadened.

The publication in 1950 by The Thoracic Society of Great Britain of the report of the ad hoc International Committee that provided an accurate description of the anatomy and a reasonable nomenclature of the bronchopulmonary segments was a marker of the maturing of thoracic surgery that peaked in the 1950s. The reporter of this agreement, Russell C. Brock, was responsible for much of its anatomic accuracy. His meticulous anatomic dissections and detailed preparation of illustrative material represents a paradigm of surgical anatomic research. It was fitting that Brock was the recorder of the occasion indicating that lung surgery had now reached the zenith of its development.

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Solitary Squamous Cell Papilloma of the Trachea

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We report a case of solitary squamous cell papilloma of the trachea and review 55 other previously reported cases. A 69-year-old man was admitted to our hospital with hemoptysis. Bronchoscopy demonstrated a papillomatous tumor diagnosed as a squamous cell papilloma. A circumferential resection of the trachea with end-to-end anastomosis was carried out. The patient's postoperative course was uneventful. From the review, there

seems to be no considerable difference in the prognoses between the endoscopically and surgically managed groups. The following indications for surgical management of solitary tracheobronchial papilloma are proposed: (1) wide-based tumor, (2) poorly visualized tumor by endoscopy, (3) suspicion of malignant tumor, and (4) patients not suitable for long-term follow-up.

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Squamous papilloma is the most common benign tumor of the larynx. In contrast, solitary squamous cell papilloma arising in the tracheobronchial tree is quite rare. In this report, we describe a case of solitary tracheal papilloma that was managed by a circumferential resection of the trachea, and we review 55 other cases of solitary tracheobronchial papilloma previously reported.

Case Report

A 69-year-old man was admitted to our hospital with 4 months of hemoptysis and pharyngeal pain. During this period, he reported coughing up "a bulky, scab-like object." He smoked 20 cigarettes a day for 50 years and had pneumonia at 65 years of age. The chest roentgenogram revealed an opacified lesion protruding into the trachea just above the carina. Cytologic examination of the sputum demonstrated class III squamous metaplastic cells. A tomogram of the trachea showed an exophytic lesion above the carina. A computed tomographic scan showed a tumor shadow at the posterior, right wall of the trachea. Neither intrapulmonary tumors nor mediastinal lymphadenopathy were noted. Bronchoscopy demonstrated a papillomatous, wide-based tumor at the posterior right wall of the trachea, 6 cm below the vocal cords. The tumor was diagnosed as a squamous cell papilloma on histological study of the biopsy specimen.

An operation was performed through a right thoracotomy (Fig 1). The trachea was opened distal to the tumor, just above the carina, and then the left and right lungs were ventilated by an endotracheal tube and jet-ventilation catheter, respectively. We carried out a circumferential resection of the trachea including six tracheal rings with an end-to-end anastomosis. The intraoperative histological examination of the margins of the resected specimen revealed no residual tumor cells. The patient

was discharged 1 month postoperatively. His course was uneventful and he remains in good health 18 months later.

The papilloma in the right wall of the trachea was a cauliflower-like and wide-based tumor with a diameter of 22 mm at its base and a height of 7 mm (Fig 2). On microscopic examination the tumor consisted of numerous papillomatous fronds. All of these fronds were lined by hyperplastic, squamous epithelium showing moderate parakeratosis and hyperkeratosis (Fig 3). Neither carcinoma in situ nor atypia was present. The tumor was diagnosed as a solitary, squamous papilloma of the trachea. An immunohistochemical examination did not demonstrate papilloma virus infection in the specimen.

Comment and Review

Squamous cell papillomatosis is the most common benign tumor of the larynx and may spread to affect the tracheobronchial tree. In contrast, solitary squamous cell papilloma arising in the tracheobronchial tree is quite rare. We review 56 cases of solitary papilloma that have been reported in the English-language literature, including our own case. These are summarized in Table 1 [1-29]. The age of the patients ranged from 1.5 to 75 years, with the average age being 51.4 ± 15.8 years, older than that of patients with laryngobronchial papillomatosis. Forty-one patients were male and 9 were female; the sex of 6 was unknown. Papillomas were located in a lobar bronchus in 41 patients, a main bronchus in 7, the trachea in 5, and an unknown location in 3. Solitary papilloma of the trachea as well as squamous cell carcinoma of the trachea is very rare [30]. Most of 56 patients whose cases we reviewed were heavy smokers; smoking is thought to be one of the most likely causes of solitary papilloma. In our case, the patient was a heavy smoker and papilloma virus infection was not demonstrated in the resected specimen by immunohistochemistry.

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Table 1. Solitary Papilloma of the Tracheobronchial Tree

Reference	Year	Age (y)	Sex	Symptoms & Episodes	Initial Diagnosis	Site	Treatment	Outcome	Carcinoma In Situ
Ashmore [1]	1954	51	F	Cough, hemoptysis	Pneumonia	RLLB	Lower lobectomy	NM	-
Sochocky [2]	1958	45	NM	Cough, hemoptysis	SCC	RLLB	Lower lobectomy	NM	-
		41	NM	Cough, fever	SCC	RISB	Pneumonectomy	NM	-
Smith and Dexter [3]	1963	50	M	Fever	SCC	RLLB	Lower lobectomy	Well at 4 y	+ ^a
		55	F	Cough	SCC	RIB	Bilobectomy	Well at 3 y	+ ^a
		61	M	Hemoptysis	SCC	LULB	Upper lobectomy	Well at 14 y	+ ^a
		66	M	Cough	SCC	Tr ^b	Observation	Sudden death	+ ^a
		63	M	Hemoptysis	SCC	LMB	Surgical removal	Death at 2 y due to colon cancer	+ ^a
		60	M	Cough	...	LLLb	Lower lobectomy	Death at 1 y due to bronchial hemorrhage	+ ^a
		48	M	Cough, dyspnea	SCC	RULB	Upper lobectomy	Well at 3 y	+ ^a
		52	M	Cough, dyspnea	SCC	RULB	Upper lobectomy	Well at 1 y	+ ^a
Drennan and Douglas [4]	1965	56	M	Wheezing, dyspnea	Bronchitis	LLLb	Expectation	Well at 3 y	-
Jackson and Hatch [5]	1968	51	M	Fever	Pneumonia	LULB	Upper lobectomy	Recurrence at 1 y, endoscopic removal; recurrence at 2 mo, left pneumonectomy	-
		51	M	Hemoptysis	Pneumonia	RULB	Endoscopic removal	Well at 1 y	-
Laubscher [6]	1969	74	M	Cough, hemoptysis	SCC	LULB	Upper lobectomy	Well at 3 y	-
Freant and Sawyer [7]	1971	1.5	M	Wheezing, dyspnea	NM	RMB	Endoscopic removal	Recurrence at 2 y, endoscopic removal	-
		NM	NM	Hemoptysis	NM	NM	Lingula excision	NM	NM
		NM	NM	NM	NM	RMLB	Middle lobectomy	NM	NM
		NM	NM	NM	NM	NM	Endoscopic removal	NM	NM
		NM	NM	NM	NM	NM	NM	Death at bronchoscopy	NM
Abe et al [8]	1972	22	M	Abnormal on CXR	Lung T	RS3B	Surgical removal	NM	-
Vontz and Vitsky [9]	1974	48	M	Wheezing, dyspnea	Asthma	RULB	Upper lobectomy	Well at 2 y	-
Fujio et al [10]	1975	55	M	...	Bronchial T (with lung cancer)	RMLB	Pneumonectomy	NM	-
Menon et al [11]	1978	54	M	Cough, chest pain	Pneumonia	LLLb	Expectation	Well at 1 y	-
Nakahashi et al [12]	1978	45	M	Cough	Pneumonia	LULB	Endoscopic removal	NM	-
Grillo [13]	1978	NM	NM	NM	NM	NM	Sleeve resection of Tr	Well	-
Cohen et al [14]	1980	8.5	F	Wheezing	Emphysema	Tr	Endoscopic removal	Well at 1 y	-
Takagi et al [15]	1980	58	F	Hemoptysis	Bronchial T	RMLB	Middle lobectomy	Well at 1 y	-

Spencer et al [16]	1980	28	M	Cough, chest pain	Bronchial T	RULB	Upper lobectomy	Well at 18 y	-
		38	F	Fever, cough	Pneumonia	(?)ULB	Upper lobectomy	NM	-
		57	M	Cough, chest pain	NM	LLLB	Lower lobectomy	NM	+
		41	M	Cough, pyrexia	Bronchial T	LMB	Pneumonectomy	NM	+
		60	M	Abnormal on CXR	Bronchial T	LLLB	Lower lobectomy	NM	-
		34	M	Chest pain	Bronchial T	LLLB	Endoscopic removal	Well at 1.5 y	-
		59	M	Hemoptysis	Bronchitis	RLLB	Endoscopic removal	Well at 2.5 y	-
Zimmermann et al [17]	1980	56	M	Asthma attack	Pulmonary Tbc	RULB	Endoscopic removal	NM	-
Roviaro et al [18]	1981	49	M	Hemoptysis	Bronchial T	RULB	Upper lobectomy	NM	+
		57	M	Recurrent pneumonia	Bronchial T	RIB	Bilobectomy	NM	-
		59	M	Hemoptysis, dyspnea	Bronchial T	LULB	Pneumonectomy	NM	+
		65	M	Hemoptysis	Bronchial T	RULB	Upper lobectomy	NM	-
Hurt [19]	1984	65	F	NM	NM	(?)MB	Endoscopic removal	Well at 15 y	-
Takase et al [20]	1984	53	M	Cough, hemoptysis	Pneumonia	LLLB	Endoscopic removal	No change at 1 y	-
Maxwell et al [21]	1985	74	M	Cough, dyspnea	Bronchitis	RLLB	Lower lobectomy	Well at 3 y	-
Rivera et al [22]	1986	3	M	Asthma attack	Asthma	Tr	Surgical removal	Recurrence at 1 y	-
Kasamatsu et al [23]	1986	75	M	Fever, cough	Pneumonia	LULB	Endoscopic laser therapy	Sudden death due to duodenal ulcer perforation	+
Barzo et al [24]	1987	49	M	NM	NM	RMB	Endoscopic removal	Well at 9 y	-
		65	M	NM	NM (with lung cancer)	RULB	Endoscopic removal	Death at 4 y due to cancer	-
		53	M	NM	NM	LMB	Endoscopic removal	Well at 3 y	-
		58	M	NM	NM	LLLB	Endoscopic removal	Well at 3 y	-
		54	M	NM	NM	RLLB	Endoscopic removal	Well at 1 y	-
Usui et al [25]	1987	66	F	Hemoptysis	Atelectasis	LB6B	Observation	No change at 2 y	NM
Niimi et al [26]	1987	60	F	Abnormal on CXR	Papilloma	RMLB	Middle lobectomy	NM	-
Trillo and Guha [27]	1988	45	M	Cough, hemoptysis	Bronchial T	RULB	Upper lobectomy	NM	-
Aota et al [28]	1988	63	M	Wheezing, dyspnea	Pulmonary Tbc	LMB	Sleeve resection of bronchus	Well at 2 y	-
Greene et al [29]	1990	48	M	Cough, chest pain	Pneumonia	RMLB	Endoscopic therapy	Well at 2 y	-
Present report	1993	69	M	Hemoptysis, pharyngeal pain	Tracheal T	Tr	Sleeve resection of Tr	Well at 1.5 y	-

^a Low-grade malignancy.^b Carina.

CXR = chest roentgenogram; IB = intermediate bronchus; L = left; LLLB = lower lobe bronchus; MB = main bronchus; NM = not mentioned; right; SCC = squamous cell carcinoma; T = tumor; Tbc = tuberculosis; Tr = trachea; ULB = upper lobe bronchus.

MLB = middle lobe bronchus; R =

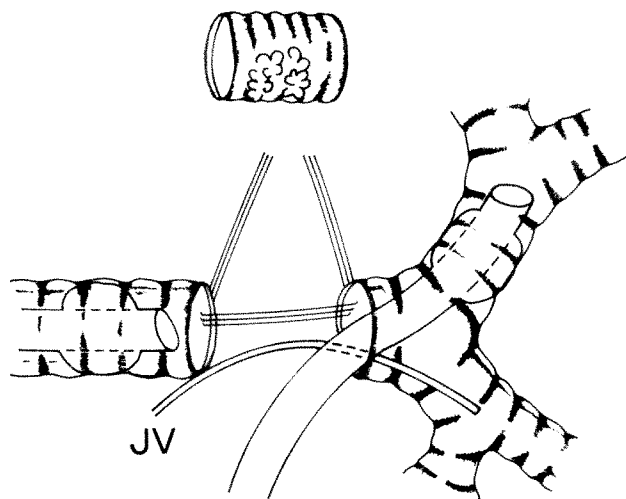


Fig 1. Schema of the operative method. (JV = jet ventilation catheter.)

In 48 cases of bronchial papilloma, pneumonectomy was performed in 4 patients, lobectomy in 23, resection of the tumor in 2, circumferential resection of the bronchus in 1, endoscopic removal in 5, and miscellaneous procedures in 3. In 5 cases of tracheal papilloma, 1 surgical resection, 2 circumferential resections of the trachea (including our case), and 1 endoscopic removal were performed; the fifth patient with tracheal papillomas died

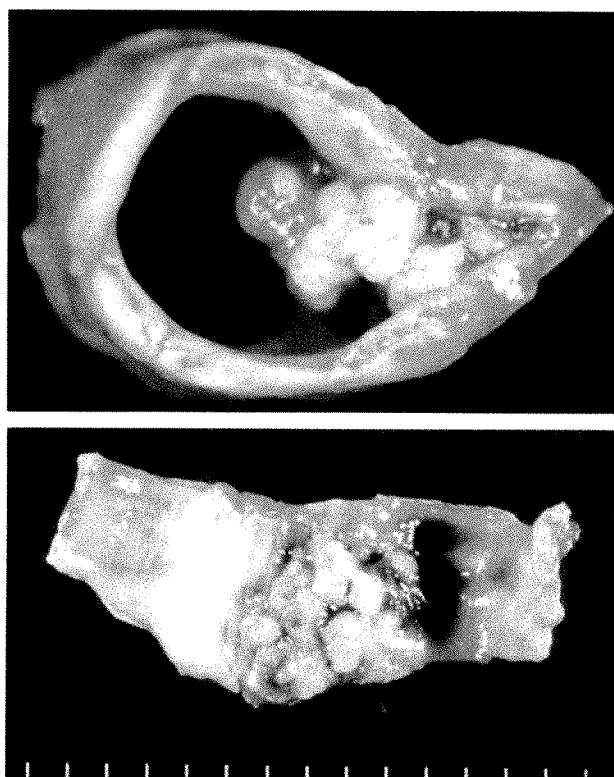


Fig 2. Macroscopic view of the circumferentially resected trachea with a solitary papilloma.

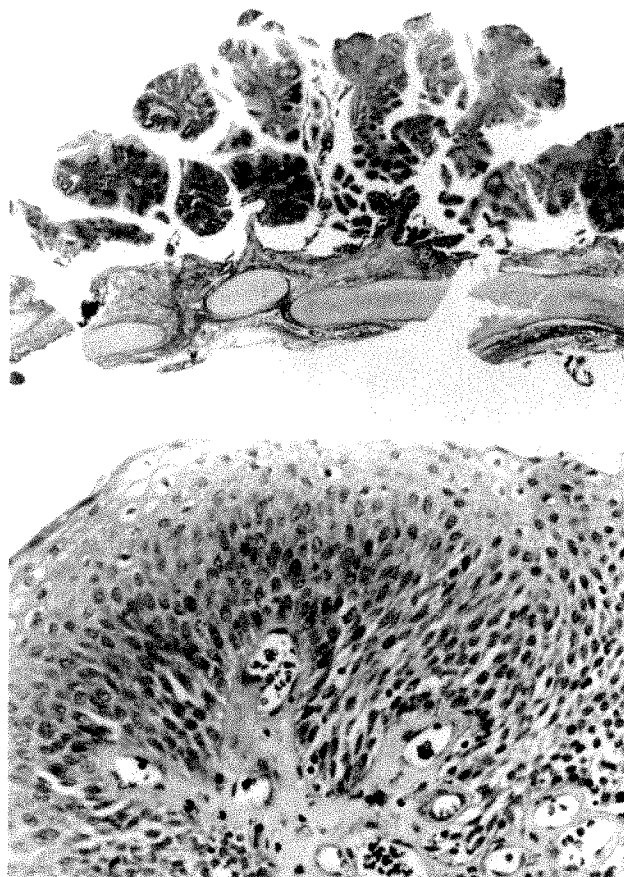


Fig 3. Microscopic view of the resected specimen. (Top) Papillomatous processes are lined by feebly keratinized squamous epithelium. (Hematoxylin and eosin, low magnification). (Bottom) The squamous epithelial lining of the papillary processes shows mild dysplasia but no malignancy. (Hematoxylin and eosin, high magnification).

suddenly during observation. The procedures performed in 3 patients are not known. As shown in Table 2, endoscopic therapy has become more frequent, although surgical management was employed in more than half of the cases in the new era. Approximately half of all cases between 1980 to 1990 [14-29; present our case] were managed endoscopically. We expect that as endoscopic therapy improves, more of these tumors will be managed endoscopically in the future.

In terms of prognosis, defining recurrence and death of any cause after surgical or endoscopic management as the postmanagement events, there were 4 events (2

Table 2. Changes in Management^a

Era	Endoscopic Therapy	Surgical Management	Miscellaneous
Old era (1954-1979)	4	18	4
New era (1980-1991)	13	14	1

^a Difference between old era and new era: $p < 0.05$ by χ^2 test.

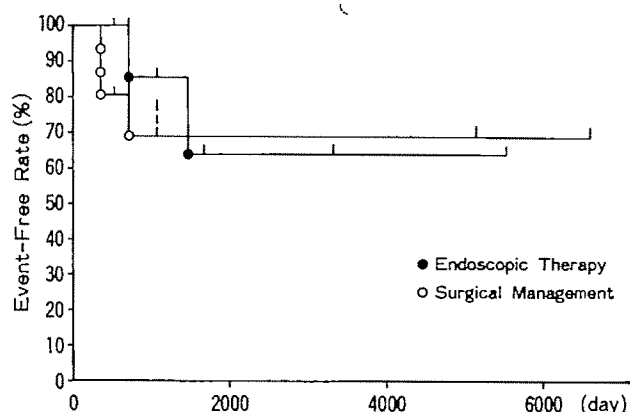


Fig 4. Actuarial event-free rate of the endoscopically and surgically managed groups. There was no significant difference between the groups.

deaths due to cancer and bronchial hemorrhage and 2 recurrences) in 16 surgically managed patients and 3 events (2 deaths due to perforation of duodenal ulcer and lung cancer and 1 recurrence) in 14 endoscopically managed patients. In addition, there is no significant difference in the event-free rate between the endoscopically managed group and the surgically managed group (Fig 4). This suggests that endoscopic therapy is as effective as operation.

In our case, we initially debated whether to perform endoscopic or surgical resection of the tumor. However, the tumor was wide-based and therefore seemed poorly suited for endoscopic extirpation. We have performed more than 30 circumferential resections of the trachea for thyroid cancer invading the trachea without any serious tracheal complications. Grillo and Mathisen [31] reported that primary tracheal tumors were able to be safely managed by the tracheal resection with primary reconstruction. Therefore, we felt comfortable in electing to perform a circumferential resection with end-to-end anastomosis to obtain a sufficient margin.

If a tracheal tumor is malignant, tracheal resection is necessary. However, nonsurgical and endoscopic management is recommended if the tumor is benign, its location seems suited for endoscopy, and repeated therapy is possible. We, therefore, propose the following indications for surgical management of solitary papilloma arising in the tracheobronchial tree: (1) the tumor is wide-based; (2) endoscopic therapy is difficult because the tumor is located in an area where it is poorly visualized; (3) it is suspected that the tumor is malignant on histological examination; and (4) it is difficult to carry out long-term follow-up of the patient, whether due to economic, geographic, or psychological problems. In our patient, surgical management was indicated by the first criterion. He underwent a circumferential resection of the trachea with end-to-end anastomosis. His postoperative course has been uneventful.

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Conduits for Coronary Artery Bypass

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Retrograde Warm Blood Cardioplegia

To the Editor:

As the lead author of the article entitled, "Retrograde continuous warm blood cardioplegia: a new concept in myocardial protection" [1], I would like to bring to the attention of the readership of *The Annals of Thoracic Surgery* an overlooked study by Gott and associates in 1957 [2]. In this experimental study, Gott and associates combined retrograde continuous blood perfusion with potassium citrate (Melrose's solution)-induced cardiac asystole to reduce myocardial oxygen demands and extend the safe duration of retrograde blood perfusion. They demonstrated that the mortality of dogs undergoing retrograde blood perfusion for 30 minutes was reduced by 50% if blood cardioplegic arrest was induced simultaneously. "On the basis of these experimental studies . . . the combination of retroperfusion and potassium asystole appears valuable for precise, direct vision reparative procedures upon the aortic valve or coronary arteries in a quiescent operative field" [2].

Hence, it appears to me that the concept of retrograde continuous normothermic blood cardioplegia and the underlying framework of what is now called "warm heart surgery" is, in fact, not new and should be properly credited as an evolution of the pioneering work of Dr Lillehei's group.

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Reply

To the Editor:

Doctor C. Walton Lillehei and I appreciate the foregoing letter from Dr Salerno to the editor regarding our use, in 1957, of combined retrograde coronary blood perfusion in combination with potassium citrate cardioplegia [1].

I had the good fortune of working as a research fellow in Dr Lillehei's cardiac surgical laboratory from the fall of 1955 through 1956. With the availability of the DeWall-Lillehei bubble oxygenator in the summer of 1955, Lillehei and his team were ready to attempt direct-vision repair of the diseased mitral valve and aortic valve, something that had not been feasible with cross-circulation. We initially evaluated, in the canine preparation, continuous antegrade perfusion using coronary cannulas, but this had the obvious disadvantage of partially obscuring the operative field and, also, the possibility of coronary ostial damage.

We became aware that Pratt [2] in 1898 had been able to support the excised cat heart for a few minutes with retrograde perfusion. Also, Blanco and associates [3] had reported on successful support of the canine heart for up to 7¼ minutes using retrograde perfusion.

After working on the technique of warm retrograde perfusion in the animal laboratory for several months, Dr Lillehei and his operative team used this technique on the first individual to have direct-vision operative repair for aortic stenosis at the University of Minnesota Hospital. At the time of this patient's operation (January 31, 1956) a small separate pump was set to deliver 125 mL of oxygenated blood per minute, and a direct-vision aortic valve commissurotomy was carried out with debridement of calcium from the valve. The total duration of the cardiopulmonary bypass run was 15¼ minutes, and the myocardium was nourished for 11 minutes by retrograde coronary perfusion. This patient made an uneventful recovery; her class IV functional status was converted to class II.

Between January 31, 1956, and April 13, 1956, Dr Lillehei and his team used warm continuous retrograde perfusion in 7 patients at the University of Minnesota [4]. In addition to the first patient who had the successful repair of a stenotic aortic valve, 2 more patients underwent successful aortic valvulotomy; a fourth patient died 2 days postoperatively of apparent aortic insufficiency. Three children had retrograde perfusion for congenital defects: a 10-year-old girl had a ruptured sinus of Valsalva successfully repaired, a 7-month-old girl had a successful correction of an aorticopulmonary window but died 10 days postoperatively of diffuse bronchiolitis obliterans, and a 2-year-old child underwent an attempted arterial switch of transposition of the great vessels. Retrograde perfusion was used for 16 minutes during the 1 hour 11 minute heart-lung bypass with the pump oxygenator. Heart action was excellent during bypass and at the conclusion of the operation, but the patient died in the early postoperative period of indeterminate causes.

We determined in the research laboratory that retrograde perfusion was successful in supporting the canine heart for periods of 15 to 20 minutes. However, of 4 animals submitted to 30 minutes of retroperfusion, 3 died, apparently of irreversible fibrillation. We thought that we might be able to extend the myocardial protection beyond 30 minutes if we combined retroperfusion with asystole induced with Melrose's potassium citrate solution. As Dr Salerno indicated in his letter, the combination of potassium citrate asystole with 30 minutes of retrograde perfusion allowed for an 80% survival among 10 animals versus 60% survival in 10 animals that received 30 minutes of retroperfusion alone [1]. Interestingly, there was only a 10% survival among 10 animals who had 15 to 30 minutes of potassium citrate asystole. It is important to note, though, that the Melrose potassium citrate solution used, both experimentally and clinically in the mid-1950s, was about ten times more concentrated than Gay-Ebert solution and, therefore, had its own inherent detrimental effect.

It has been interesting to see a great deal of current interest in retrograde perfusion. This has been a logical extension of antegrade blood cardioplegia, both cold and warm. Interestingly, among the 448 abstracts recently submitted for consideration for presentation at the 1993 meeting of The Society of Thoracic Surgeons, there were 22 that dealt with newer techniques of myocardial protection. Half of these were clinical reports and the other half were from the research laboratory. The majority of the 22 reports on myocardial preservation dealt with comparison of various combinations of antegrade blood cardioplegia, both cold and warm, and retrograde cardioplegia, both cold and warm. The fact that there were so many abstracts submitted on this subject would indicate to me that many cardiac surgeons are still not totally pleased with their method of myocardial protection.

In 1974 we initiated, at The Johns Hopkins Hospital, standard intermittent crystalloid cardioplegia as recommended by Gay and Ebert [5]. In 1982 we added the significant protection factor of Stanford topical cold-saline pericardial perfusion (14 to 16 L used

during a standard triple bypass procedure). We continue to favor crystalloid cardioplegia because of its simplicity and seemingly excellent myocardial protection. We, however, seem to be, from the standpoint of myocardial protection techniques (ie, blood versus crystalloid, retrograde versus antegrade), very much in the minority.

Again, Dr Lillehei and the rest of his research and clinical team appreciate Dr Salerno's letter on this topic of retrograde coronary perfusion.

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White Matter Lesions and Heart Operations

To the Editor:

I read with interest the article by Sellman and associates [1] concerning magnetic resonance imaging of the brain. The attention to white matter lesions has been stimulated recently by reports of low density in the periventricle on x-ray computed tomographic scan [2, 3] and high signal intensity on T₂-weighted magnetic resonance imaging [4-6]. However, to our knowledge, no investigator had described the patients selected for cardiac operation who had cerebral white matter lesions. Diffuse white matter lesions are assumed to be caused by an increase in cerebral vulnerability due to harmful effects of cardiopulmonary bypass. We conducted a clinical study to define the relation between coexistent diffuse cerebral white matter lesions and neuropsychological outcome after coronary artery bypass grafting.

X-ray computed tomographic scan of the brain was performed in 104 patients, and preoperative and postoperative neuropsychological functions were evaluated. The average age was 66.8 years (range, 54 to 80 years). The patients were categorized as follows according to the computed tomographic findings: 73 patients were normal or showed slight cerebral cortical atrophy, which is usually seen in patients more 50 years of age (group 1); 16 patients showed moderate or severe cortical atrophy (group 2); and 15 patients demonstrated severe white matter hypodensity especially in the frontal horns, and dilated ventricles (group 3). Fourteen of 15 patients in group 3 were hypertensive. No patient showed neurological signs or psychiatric abnormalities at preoperative clinical examination. The anesthetic regimen used was based on a modified form of neuroleptanalgesia supplemented by muscle relaxants. Extracorporeal circulation was accomplished with pulsatile flow, and a Mera membrane oxygenator was employed. Moderate systemic hypothermia (30°C) was induced. The flow rate of the extracorporeal circulation was maintained at 2.0 to 2.5 L/m². The duration of cardiopulmonary bypass time

was 161 ± 39 minutes, and the aortic cross-clamp time was 76 ± 16 minutes. No significant difference was noted between the groups in terms of patient's age, duration of cardiopulmonary bypass, and perioperative blood pressure.

Clinically overt neuropsychological deterioration was not observed in patients in groups 1 and 2. Six patients in group 3 presented psychiatric disturbance in the form of intellectual impairment, states of confusion, and alteration of personality immediately after coronary bypass operation. A pseudobulbar palsy was also observed in 3 patients. These clinical signs of neuropsychological impairment persisted for 1 to 3 weeks, and were most often reversible.

The underlying mechanism of these deleterious alterations is not elucidated, but the ischemic nature of the characteristic white matter lesions is suspected. The periventricular area is an end zone for perforating arteries arising from the surface cerebral arteries, and large white-matter lesions in deeper white matter were associated with a diffuse decrease of cortical perfusion [7]. We assume that the arteriosclerotic changes of the long cortical perforating arteries led to inadequate cerebral cortical perfusion during cardiopulmonary bypass, which is a major cause of neuropsychological dysfunction. Computed tomographic scan has proved less sensitive than magnetic resonance imaging in detecting white matter lesions, and the number of patients in our series was small [4]. This problem should be further assessed with a more detailed analysis of both cerebral cortical lesions and neuropsychological findings.

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Reply

To the Editor:

My colleagues and I appreciate Drs Iguchi and Sato's comments regarding our article about cerebral magnetic resonance imaging findings after coronary artery bypass grafting. White matter lesions were observed in 17 of our 29 patients (59%) and were not altered by extracorporeal circulation. Our patients were on aver-

age 7 years younger (mean, 60 years; range, 45 to 69 years) than those of Drs Iguchi and Sato. As white matter abnormalities are supposed to be related to aging, we find their 14.4% (15/104 patients) incidence of lesions low. Are we discussing identical white matter lesions or are there considerable variations? In contrast to Drs Iguchi and Sato, we did not correlate white matter lucencies to postoperative neuropsychological findings. We agree that magnetic resonance imaging is superior for detecting ischemic complications after extracorporeal circulation compared with computed tomography.

We plan further investigations with a so-called diffusion magnetic resonance imaging technique to detect ischemic areas during extracorporeal circulation, and also to functionally map these patients with a positron emission tomograph and simultaneous neuropsychological testing.

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"Chordal" Preservation During Mitral Valve Rereplacement

To the Editor:

Olinger [1] recently described a method for "represerving" the mitral subvalvular apparatus during rereplacement of a failed mitral bioprosthesis that had originally been inserted with preservation of the mitral leaflets and chordae.

Although I strongly support and practice the principle of chordal preservation during mitral valve replacement, the elegant technique described by Olinger for rereplacements seems rather time consuming, and it is not feasible if—as is so often the case—the first operation was carried out without chordal preservation.

A simpler, equally effective, and more expeditious technique for maintaining the normal relationship between the mitral annulus and the papillary muscles has been advocated by Tirone David, MD, for several years, and I have used it many times. It is particularly helpful for rereplacements, although it is also quite suitable for initial replacements whenever preservation of the native valve is awkward or impractical, such as in patients with calcific rheumatic mitral disease.

In brief, after the native or replacement valve is excised, figure-of-8 sutures of nonabsorbable material are placed through the fibrous heads of each papillary muscle. The sutures from the anterior heads of the papillary muscles are then passed through the mitral annulus at the respective commissures. The sutures from the posterior heads are placed posterior to each commissure. The sutures are tied to fix the proper distance between the papillary muscles and the annulus. After the prosthesis is inserted in the usual manner, the ends of these tethering sutures are also passed through the sewing ring of the replacement prosthesis to transfer the stress to the prosthesis.

This technique thus simulates preservation of the "chordae." The benefits of preventing "untethering" of the left ventricle [2] are thus achieved without complex, time-consuming maneuvers, and without the risk of left ventricular outflow obstruction.

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Direct Mechanical Ventricular Actuation

To the Editor:

I was happy to read the recent article by Lowe and associates [1] entitled "First successful bridge to cardiac transplantation using direct mechanical ventricular actuation." This concept was developed by my colleagues and I in the 1960s for resuscitating an arrested heart and published in the *Indian Journal of Surgery* [2, 3]. We developed a cardiac assisting device for pulsating the heart during cardiac arrest and found this principle very effective in animal subjects. I am very happy to note that the same principle has now been used as a bridge to cardiac transplantation.

My heartiest congratulations to the authors of this article, who have found it effective for heart transplant patients waiting for a suitable donor heart.

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Reply

To the Editor:

We appreciate Dr Khanna's comments concerning our article. Doctor Khanna's cited publications demonstrate that he experimented with a device similar to direct mechanical ventricular actuation (DMVA). We feel compelled to point out, however, that George L. Anstadt, VMD, first described and successfully developed this technology in the 1960s, years before Dr Khanna and associates published their two manuscripts.

In 1945, George L. Anstadt witnessed his father's sudden death due to a massive heart attack. Later that year, his attention was drawn to a picture of the iron lung on the cover of *Life* magazine, and he contemplated how he could apply this concept to the arrested heart. It is interesting that to this day he likens his heart cup to an "iron lung" for the heart. The initial DMVA experiments took place at the USAF School of Aerospace Medicine, San Antonio, Texas, from 1960 to 1962. During this time, Dr Anstadt bonded surgical gloves inside modified aluminum funnels to make a prototype of the concept. Explanted canine hearts were aspirated into the crude devices by means of a vacuum delivered through the funnel's spout. The funnel-housed glove was then pneumatically inflated and deflated to actuate the

asystolic heart. These experiments represent the earliest bench testing of DMVA.

Doctor Anstadt subsequently wrote and successfully defended his thesis, "A study in the development of an effective method of direct mechanical ventricular assistance" at the University of Pennsylvania (Sep 1963-Aug 1965). He gave the first public presentation of DMVA at the 38th Scientific Sessions of the American Heart Association [1]. More than 50 subsequent publications have reported successful utilization of his method in both laboratory and clinical settings [2].

Although various mechanical cardiac compression devices have been described by other investigators [3-7], no method other than DMVA uses a uniquely nontraumatic means of application (a vacuum) and effectively participates in the diastolic phase of the cardiac cycle.

Ongoing investigations at Duke University Medical Center are aimed at testing DMVA for long-term circulatory support. Recent clinical applications have been restricted to well-selected patients in either refractory cardiac arrest or failure who meet selection criteria for cardiac transplantation. Even if the cardiac failure is irreversible, an eventual therapeutic end-point is still possible. Although bridging to transplantation may be viewed as a new application for DMVA, the inventor, George L. Anstadt, VMD, realizes it is simply a prolonged exercise in resuscitative circulatory support.

We appreciate Dr Khanna's supportive letter regarding our recent success, but wish to emphasize that Dr Anstadt deserves recognition for first describing DMVA and subsequently developing it to its current state. Doctor Anstadt's dedication of personal time and effort to this technology has persisted for more than 30 years. We hope that ongoing efforts at Duke University will demonstrate the broad clinical potential for this very unique and promising technology, which provides non-blood contacting, biventricular, total circulatory support.

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Intraaortic Balloon Position

To the Editor:

I read with particular interest the article published in the April issue of *The Annals* [1] entitled "Effects of Intrathoracic balloon

position on renal artery blood flow." My interest is due to the fact that in my 61-patient experience with right gastroepiploic artery (RGEA) for myocardial revascularization, I had 2 patients in whom I had to insert an intraaortic balloon pump. In those patients the RGEA was used to bypass the posterior descending branch of the right coronary artery, and a postoperative inferior myocardial infarction occurred, as documented by electrocardiogram and creatine kinase-MB level. Angiography performed 1.5 months after operation showed a patent RGEA graft.

Do you think, as I do, that the intraaortic balloon pump influences the flow in the RGEA? Although the explanation could be based on a spasm due to the characteristics of a muscular artery such as the RGEA, I would like very much to hear your opinion on that subject.

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Ionescu-Shiley Standard-Profile and Low-Profile Valves To the Editor:

The recent companion articles [1, 2] on failed Ionescu-Shiley standard-profile and low-profile valves contain valuable information about tissue failure mechanisms and valve design. However, there is a problem with the reasoning used to justify their conclusion [2] that: "... low-profile valves ... fail after a shorter time in situ than their standard-profile counterparts, at a mean of 45.1 months versus 78.0 in the aortic position ($p < 0.01$) and at 52.2 months versus 73.8 in the mitral position ($p < 0.05$)."

The problem is that the standard-profile valves were implanted earlier and followed up for a longer time, on average, than the low-profile valves. The mean time to failure in an ongoing series will depend on the amount of time the series has been followed up and will, in general, be larger in longer series that are otherwise similar.

In Table 1, the mean failure times are weighted combinations of those given above for both positions and converted to years. For both valve models, the mean failure time is about 75% of the midpoint of the range of potential follow-up years. Thus, this very crude method of adjusting for the differences in follow-up times completely accounts for the apparent difference in mean failure times. A proper way to compare failure times is to use the

Table 1. Relationship of Failure Times to Follow-up Years

Variable	Standard-Profile	Low-Profile
Mean failure times (y)	6.4	4.0
Implant dates	4/77-6/86	12/81-8/88
Follow-up date	7/1/90	7/1/90
Potential follow-up years	4.1-13.3	1.9-8.6
Midpoint of follow-up years	8.7	5.3

actuarial method, as their group did in their previous excellent review of these series [3].

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3. Masters RG, Pipe AL, Bedard JP, et al. Long-term clinical results with the Ionescu-Shiley pericardial xenograft. *J Thorac Cardiovasc Surg* 1991;101:81-9.

Reply

To the Editor:

We would like to thank Dr Grunkemeier for his thoughtful comments on our article [1]. In our view, there is substantial overlap in the implanted times of the standard-profile and low-profile valves from the series. As noted by Dr Grunkemeier, the appropriate manner in which to analyze failure time data is using actuarial methods. Unfortunately, not all of the necessary data were available to us; therefore, we used a crude analysis, independent Student's *t* tests, to address the important question "were there differences in in-situ times between standard-profile and low-profile valves?" As mentioned in our article, the more extensive clinical analysis from this series has previously been published [2].

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References

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2. Masters RG, Pipe AL, Bedard JP, et al. Long-term clinical results with the Ionescu-Shiley pericardial xenograft. *J Thorac Cardiovasc Surg* 1991;101:81-9.

Thoracoscopic Excision of Bronchogenic Cysts

To the Editor:

We found the current review on asymptomatic bronchogenic cysts by Bolton and Shahian [1] to be both an interesting and

useful treatise. However, in our minds, the management comments of the review are probably already outdated. We believe that thoracoscopic removal of all types of mediastinal cysts can be accomplished in most patients without thoracotomy, using the same surgical caveats that one would use in an open technique. Lewis and associates [2] reported a video-assisted technique that also accomplishes the same results. Thoracoscopic excision of mediastinal cysts is rapidly becoming accepted as a standard surgical treatment.

Because a less invasive method to reliably diagnose and definitively treat bronchogenic cysts now exists, the threshold for recommending treatment of bronchogenic cysts should probably also change. We certainly believe that the morbidity of thoracoscopy better matches the morbidity of the disease process than does thoracotomy. Because the review did not address the expanded role of thoracoscopy in the management of bronchogenic cysts, do Bolton and Shahian believe their recommendations should change? Specifically, in view of a less invasive approach, when do Bolton and Shahian believe that thoracoscopic removal of a cyst is preferable to long-term observation?

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Reply

To the Editor:

We agree with Drs Acuff and associates that imaged thoracoscopic surgery may be very useful for the removal of some bronchogenic cysts, and we mention this specifically in our article. This technique may be employed for the diagnosis and treatment of enlarging, symptomatic, or atypical cystic lesions. However, the fact that a less invasive procedure exists does not necessarily constitute an indication for operation. There is still a role for observation of small, classic asymptomatic bronchogenic cysts.

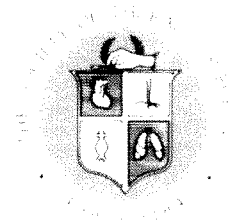
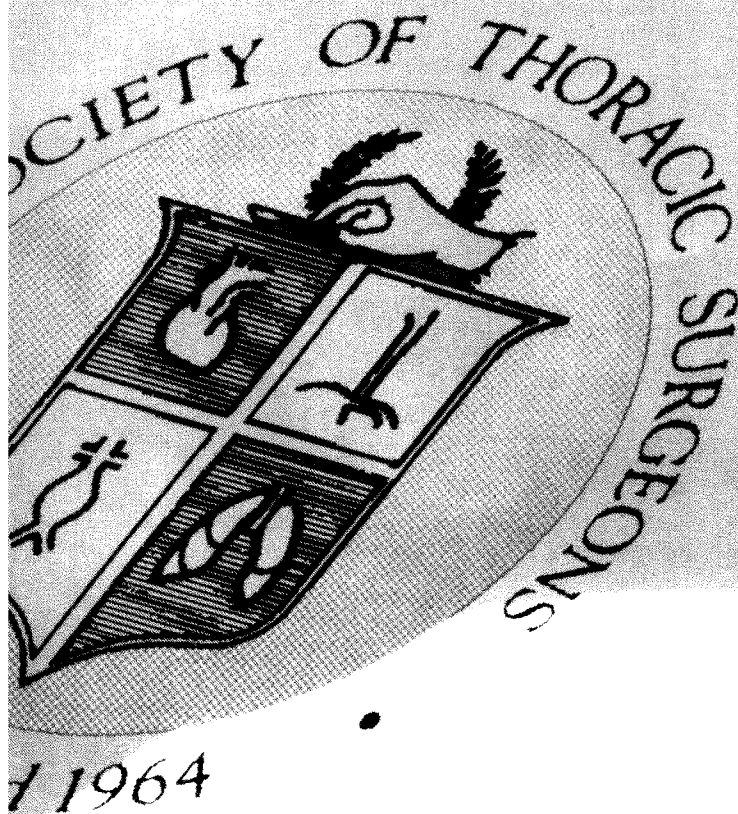
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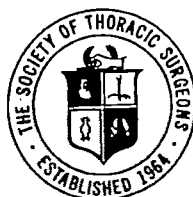
Circulatory Support 1991

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Circulatory Support 1991



On November 16 and 17, 1991, in San Francisco, a special session entitled "Circulatory Support 1991" sponsored by The Society of Thoracic Surgeons featured presentations summarizing current practices with circulatory support devices of all types. International experts from clinical, engineering, industrial, and regulatory disciplines met and exchanged experiences and opinions. Formats for presentation included formal presentations, panel discussions, and focused "break-out" groups. Most of the information from that meeting is presented in this supplement to *The Annals of Thoracic Surgery*. It consists of scientific papers, "state of the art" summaries, transcribed and edited panel discussions, and position papers of industry, clinicians, the Food and Drug Administration, and the FDA Devices Panel.

This meeting was planned as a sequel to Circulatory

Support 1988 by the STS Ad Hoc Committee on Circulatory Support Devices, including D. Glenn Pennington (Chairman), Bartley P. Griffith, Charles-Julien Hahn, J. Donald Hill, Larry R. Kaiser, George J. Magovern, Walter E. Pae, Peer M. Portner, Glenn Rahmoeller, and myself. I would like to thank the committee members, the other participants, and the discussants for their efforts to make the meeting and the record of the meeting a dynamic exchange of ideas and a point of reference for the future. I would also like to thank The Society of Thoracic Surgeons for their leadership in supporting the meeting and the supplement, and the editorial office of *The Annals* for their help.

Jack G. Copeland III, MD
Guest Editor

Program

■ Saturday, November 16, 1991

8:00–8:15 **Welcome and Opening Remarks**
D. Glenn Pennington, Chairman, Ad Hoc Committee on Circulatory Support and Thoracic Transplantation of The Society of Thoracic Surgeons

Problem Case Oriented Panels

8:15–8:55 **Panel I: Patient Selection***
Moderator: D. Glenn Pennington, St. Louis, MO
Panelists: David J. Farrar, San Francisco, CA
Daniel Loisançe, Paris, France
Walter E. Pae, Jr, Hershey, PA
Robert W. Emery, Minneapolis, MN

8:55–9:15 **Registry Report***
Walter E. Pae, Jr, Hershey, PA

9:15–10:05 **Video Session I**
Discussion Leader: W. Gerald Rainer, Denver, CO

10:05–10:50 **Break**
Visit Exhibits/Posters

10:50–11:40 **Video Session II**
Discussion Leader: Wilbert J. Keon, Ottawa, Canada

11:40–12:30 **Video Session III**
Discussion Leader: Ernst Wolner, Vienna, Austria

12:30–1:30 **Luncheon**

1:40–2:40 **Three Breakout "How To" Panels—Session I**

1. Nonpulsatile Circulatory Support: Techniques of Insertion*
Moderator: George J. Magovern, Jr, Pittsburgh, PA
Panelists: Richard K. Wampler, Rancho Cordova, CA
Lyle D. Joyce, Minneapolis, MN
Thomas H. Wareing, St. Louis, MO

2. External Pulsatile Circulatory Support
Moderator: J. Donald Hill, San Francisco, CA

Panelists: Yukiyasu Sezai, Tokyo, Japan
Roland Hetzer, Berlin, Germany
Robert A. Guyton, Atlanta, GA

3. Internal Pulsatile Circulatory Support*
Moderator: Peer M. Portner, Oakland, CA

Panelists: William A. Baumgartner, Baltimore, MD
Christian Cabrol, Paris, France
O. H. Frazier, Houston, TX

1:40–2:40

Cardiac Nursing Breakout Session
Nursing Care of the Patient on Mechanical Circulatory Support*
Moderator: Julie A. Shinn, Stanford, CA

1. Transfer of VAD Patients to Non-Critical Care Areas
Nancy Abou-Awadi, Houston, TX
2. Nutritional Support and Activity Guidelines
S. Jill Ley, San Francisco, CA
3. Infection Control Measures
Jane Reedy, St. Louis, MO
4. Psychosocial Aspects of Care
W. Donald Rountree, Louisville, KY

2:45–3:45

Three Breakout "How To" Panels—Session II

1. Nonpulsatile Circulatory Support
Moderator: George Paul Noon, Houston, TX
Panelists: Jack J. Curtis, Columbia, MO
Charles Henry Moore III, San Antonio, TX
Michael S. Sweeney, Houston, TX
2. External Pulsatile Circulatory Support*
Moderator: Charles-Julien Hahn, Arzier, Switzerland
Panelists: William L. Holman, Birmingham, AL

* This presentation is published in this special section.

- Jack G. Copeland III, Tucson, AZ
Gerard Champsaur, Lyon, France
3. Internal Pulsatile Circulatory Support
Moderator: Philip E. Oyer, Stanford, CA
Panelists: Robert L. Kormos, Pittsburgh, PA
Terence Lewis, London, England
Roque Pifarre, Maywood, IL
- 3:45–4:30 **Break**
Visit Exhibits/Posters
- 4:40–5:10 **Panel II: Anticoagulation***
Moderator: Jack G. Copeland III, Tucson, AZ
Panelists: O. H. Frazier, Houston, TX
Lawrence R. McBride, St. Louis, MO
Marko Turina, Zurich, Switzerland
Christian Cabrol, Paris, France
- 5:10–5:50 **Panel III: Infections—Prophylaxis and Treatment***
Moderator: J. Donald Hill, San Francisco, CA
Panelists: Bartley P. Griffith, Pittsburgh, PA
Marco Meli, Sion, Switzerland
Paul Didisheim, Bethesda, MD
- 5:50–6:30 **Panel IV: Management of Secondary Organ Dysfunction***
Moderator: William S. Pierce, Hershey, PA
Panelists: James J. Hershon, San Francisco, CA
Robert L. Kormos, Pittsburgh, PA
Walter P. Dembitsky, San Diego, CA
George Paul Noon, Houston, TX
- 6:45–7:45 **Welcome Reception**

■ Sunday, November 17, 1991

- 6:40–7:40 **Special Breakfast Panel V: Long-Term Biventricular Assist***
Moderator: Charles-Julien Hahn, Arzier, Switzerland
Panelists: William S. Pierce, Hershey, PA
Don B. Olsen, Salt Lake City, UT
Kenneth Butler, Rancho Cordova, CA
Robert T. V. Kung, Danvers, MA
- 7:45–9:20 **State of the Art I**
Moderator: Frank C. Spencer, New York, NY

1. Emergency Resuscitation Using Portable Extracorporeal Membrane Oxygenation*
Walter P. Dembitsky, San Diego, CA
2. Circulatory Support With Heparinless CPB
Per Olsson, Stockholm, Sweden
3. Hemopump: Clinical Results and Applications
Richard K. Wampler, Rancho Cordova, CA
4. The Biopump and Postoperative Circulatory Support*
George J. Magovern, Jr, Pittsburgh, PA
5. Clinical Experience With Ventricular Assist Systems in Japan*
Hisateru Takano, Osaka, Japan

- 9:20–10:05 **Break**
Visit Exhibits/Posters

- 10:05–11:40 **State of the Art II**
Moderator: Michael E. DeBakey, Houston, TX
6. Optimizing Hemodynamics and Assessing Myocardial Recovery
George Paul Noon, Houston, TX
 7. Circulatory Support With Shock due to Acute Myocardial Infarction*
Ernst Wolner, Vienna, Austria
 8. Circulatory Support in Infants and Children*
D. Glenn Pennington, St. Louis, MO
 9. World Experience With Skeletal Muscle Cardiac Assist
James A. Magovern, Pittsburgh, PA
 10. Current Expectations in Dynamic Cardiomyoplasty*
Adib D. Jatene, Sao Paulo, Brazil

- 11:40–12:00 **Break**
Visit Exhibits/Posters

- 12:00–1:35 **State of the Art III**
Moderator: Norman E. Shumway, Stanford, CA
11. Right Heart Management During LVAD Support
Bartley P. Griffith, Pittsburgh, PA
 12. Univentricular and Biventricular Thoratec VAD Support as a Bridge to Transplantation*
J. Donald Hill, San Francisco, CA

* This presentation is published in this special section.

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13. Bridge to Transplantation With the Symbion J7 TAH
Christian Cabrol, Paris, France
 14. Chronic Left Ventricular Support With a Vented Electric Assist Device*
O. H. Frazier, Houston, TX
 15. Chronic Support With the Novacor LVAS
Peer M. Portner, Oakland, CA

1:35 **Close of Main Session**

2:30-4:00

FDA Regulatory Issues Session

How Much Do We Need to Know Before Approving a Ventricular Assist Device?*

Moderator: J. Donald Hill, San Francisco, CA

Panelists: Bette Lemperle, FDA Reviewer

Mark Levinson, FDA Advisory Committee Member

Victor L. Poirier, Industry Perspective (Thermo Cardiosystems, Inc)

Bartley P. Griffith, Clinical Perspective

4:00-5:00

Question and Answer Session

* This presentation is published in this special section.

Panel I

Patient Selection

Moderator: D. Glenn Pennington, MD

Panelists: David J. Farrar, PhD, Daniel Loisance, MD, Walter E. Pae, Jr, MD, and Robert W. Emery, MD

MODERATOR PENNINGTON: Our first session is entitled "Patient Selection." Many of us believe this is the key to the appropriate use of these devices. There is much to learn about patient selection even today after several years of working with these devices. It has been estimated that in the United States there are 250,000 cardiac surgical procedures performed per year. Somewhere between 1% and 7% of those patients require an intraaortic balloon pump. Of those receiving an intraaortic balloon after a cardiac operation, about 65% survive. However, fewer than 1% of patients receive a ventricular assist device (VAD) [1]. Therefore, it appears that we are under-using our capability with these systems. This suggests to me that postcardiotomy is one of the areas that needs reevaluation of our use of these systems.

How does the use of assist devices compare with conventional treatment in our cardiac transplant population? We have struggled with the notion that patients requiring circulatory support would be less than optimal candidates for transplantation. But when we reviewed our own series and looked only at status 1 patients, that is, patients who were supported with mechanical devices such as a VAD as opposed to those supported with drugs and a balloon pump, we found that the VAD patients had lower mortality rates both initially and in the follow-up. So it appears that some of the patients we are supporting with "conventional" measures, including intraaortic balloon pumping, might be better served by ventricular assist device support [2]. Daniel Loisance will take me to task about that later on in our discussion.

I would like to introduce our first panelist, Walter Pae, who will cover the question of how to select patients for postcardiotomy support.

DR PAE: Thank you, Dr Pennington. Doctor Pennington has asked me to briefly deal with patient selection in regard to postcardiotomy cardiogenic shock and aggressive circulatory support. I might preface this by saying that perhaps in this particular area, despite a very, very large clinical experience, more is known regarding who is at risk of not surviving than the converse. Despite the recent advances in myocardial preservation and the techniques in cardiac surgery in general, we all recognize that we are operating on high-risk patients. These risks tend to offset the improvements and lead to a reported steady incidence of postcardiotomy cardiogenic shock, which, as

mentioned, occurs in somewhere between 1% and 7% of all patients who undergo cardiac surgical procedures.

Now I believe a consensus exists among most cardiac surgeons that after a cardiac operation a cardiac index of less than 1.7 to $2.0 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ coupled with elevated systemic vascular resistance and pulmonary capillary wedge pressure along with arterial hypotension carries a very high probability of cardiac death. However, despite the efficacy of inotropic drugs and the intraaortic balloon to "reverse this low output syndrome," or improve the hemodynamic parameters in 75% to 85% of patients, survival is still widely variable and reported in the literature to be in the 30% to 65% range. I believe the issue in terms of patient selection, given the relative safety and efficacy of the current devices, is at what point aggressive circulatory support should be instituted. How much drug therapy in addition to the intraaortic balloon should be "tolerated" by the surgeon to the detriment of the myocardium and other organ systems to achieve "suitable hemodynamics," only to have an unsuitable patient outcome? Unfortunately, at this time, there is a large gap in our knowledge, and appropriate clinical studies are really needed to answer these pivotal questions. It is certainly reasonable to hypothesize that the outcome in these critically ill patients will be improved if circulatory support is instituted earlier but not inappropriately. Hopefully in the discussion some of these issues can be addressed.

In the next session, encompassing the registry report, I will attempt to detail a number of issues regarding patient selection in relation to survival in both postcardiotomy cardiogenic shock and the bridge to transplantation application. However, I would like to emphasize certain points here as well. In this relatively large database there are certain themes that are recurrent. First, the outcome appears to be unrelated to the original operative procedure. Although the rates of weaning from devices after cardiotomy does not differ statistically, there is a decreasing probability of hospital discharge in those patients more than 70 years of age. This would indicate that although myocardial recovery occurs, the physiological reserve is quite limited in the elderly population, leading to only an overall 13% salvage rate in this particular age group [3]. Now, severe biventricular failure and perioperative infarction alone or in combination are very powerful predictors of ultimate survival [4-6]. Some investigators, including our illustrious moderator, have stated that unless a patient is a transplant candidate they would not institute postcardiotomy ventricular assist under the

circumstances of known perioperative infarction and severe biventricular failure. Unfortunately, although biventricular failure is easy to diagnose at operation, perioperative myocardial infarction may be considerably more difficult to establish intraoperatively. Finally, although not precisely patient related, bleeding remains a powerful negative predictor of survival and seems to be more highly associated with vortex pump systems. Although prolonged cardiopulmonary bypass has multiple organ effects, certainly increased bleeding is a well-recognized complication, and poor results are seen with longer bypass times of 4 to 6 hours. Therefore the ideal patient, although difficult to find, is less than 70 years old, has had a technically satisfactory operation, does not have any preexisting organ dysfunction, and has had a short cardiopulmonary bypass time. Univentricular failure predominates and perioperative infarction is unlikely. I think I will stop here to keep within the time constraints and to allow for some discussion.

MODERATOR PENNINGTON: We will have our discussion after all of the panelists have presented. Next David Farrar will give us some thoughts about choosing the bridge to transplantation patient.

DR FARRAR: Thank you, Dr Pennington. I would like to speak to you briefly as the study monitor for the Thoratec VAD. It is very clear to me after reviewing all the patients in our study and talking to all the investigators that we might even list the three most important factors as patient selection, patient selection, and patient selection [7]. However, let us not forget early VAD implantation, to which Dr Pae alluded, which may even be more important. One of the problems we have, of course, in evaluating the data is how to quantitate factors of patient selection so these can be submitted to the Food and Drug Administration and examined for reasonable variables. This is, indeed, a very difficult thing to do, particularly on an individual patient basis. It is pretty easy to say that the ideal candidate for bridging to cardiac transplantation is somebody who has single organ disease. The patient we would like to bridge has irreversible heart failure before any irreversible failure of end-organ function and no contraindications to heart transplantation. The difficulty appears to be in determining when irreversible failure of end-organ function has occurred that would contraindicate use of a VAD.

I would like to discuss briefly a few things we have done looking at preoperative variables in our database, which consists of 151 patients who were implanted with a Thoratec VAD for bridging to transplantation: 118 male and 33 female patients. The average age is 42 years, with a range of 11 to 64 years. There is a wide range in weight, from the smallest patient of 30 kg to the largest of 123 kg. Sixty-three of these patients had coronary artery disease, 73 had nonischemic cardiomyopathies, 8 were posttransplantation, and 7 had other cardiac disease. We looked at some of the preoperative variables in this patient population and tried to retrospectively determine in the patients who died the effect of preoperative variables. Thirty-five

percent of the patients died before transplantation—the largest mortality. Only 16% died after transplantation, so there is an 84% posttransplantation survival. There were 82 survivors after transplantation, 54% of the total in whom a VAD was implanted.

Are there any preoperative variables that can predict why patients died before transplantation? If we look at 15 potential risk factors in our database—age, sex, body surface area, diagnosis, previous operation, intraaortic balloon pump, mechanical ventilation, cardiac arrest, whether the implant was emergent or not, whether the patient came from the postcardiotomy support group as opposed to primary bridge, hemodynamics, cardiac index, pulmonary capillary wedge pressure, other system disease, blood urea nitrogen (BUN), creatinine, and bilirubin—four factors were significant: age, sex, previous operation, and BUN. Doctor Pae just alluded to the effects of age. We found an interaction between age and sex; male and female patients old and young have to be separated for these to become significant factors. Previous operation was extremely significant, as was BUN. In patients with previous cardiac operations, there was only 33% survival to transplantation, whereas those who did not have previous cardiac operations had a 67% survival to transplantation. If we divide patients above and below the median age of 42 years, there is improved survival in the younger group. Males have 77% survival and females 56% survival. But among older patients, males had a 60% survival and females had only a 30% survival. Also, there is a greater difference between older females and younger males. These are very significant risk factors. I would like to point out that I did not realize the importance of BUN until about a week or two ago when preoperative laboratory values were analyzed and we found elevated BUN to be a significant risk factor for survival. We stratified the data based on preoperative BUN and survival to transplantation. Patients with a BUN of less than 20 mg/dL preoperatively had a 75% survival; 20 to 30 mg/dL, 69%; 30 to 40 mg/dL, 62%; 40 to 70 mg/dL, 50%; and greater than 70 mg/dL, 25%. Kidney function in and of itself is not predictive in that if we look at creatinine level we do not see the same slope. If preoperative creatinine level is less than 1.5 mg/dL, survival is 66%; at 1.5 to 1.9 mg/dL, 64%, the same percent survival all the way up to a creatinine level of 3 mg/dL. At a creatinine level greater than 3 mg/dL, the survival drops off quite sharply to 25%. In summary, there are some preoperative values that do help predict success for the bridge to transplantation procedure.

MODERATOR PENNINGTON: Some of us have had the terrible problem of trying to deal with a patient after transplantation who simply did not do well and required circulatory support. Our own results have been so bad that retrospectively we would have excluded most of those patients from support. Robert Emery has some new lessons for us, and we will ask him to give those now.

DR EMERY: Thank you, Dr Pennington. The patients who have undergone transplantation, if we adhere to our

usual criteria for selecting transplant candidates, should be ideal candidates to support with mechanical devices should the organ fail, and I think the data that Drs Farrar and Pae have given support this. There are a number of reasons why a donor organ can fail when you take a supposedly healthy organ, remove it for several hours, and reimplant it. High pulmonary vascular resistance is a recipient-mediated factor, as are others, including a previous cardiac operation with technical difficulty or the removal of a bridge device with adhesions that make the implantation procedure difficult, preoperative cardiac medications such as amiodarone, or multiorgan system failure in patients before transplantation. Procurement or donor-mediated factors for failure of the donor heart include premortem myocardial injury, preservation injury, unknown sepsis in the donor, prolonged ischemic time, the use of a "nontraditional" donor, and deleterious effects of a multiple organ harvest. The latter I think is very important, having noticed substantial difference in cardiac recovery from the days when we used to just remove the heart and the kidneys to the present time when organ harvest is a 4- or 5-hour operation for the general surgeons to remove the liver, kidneys, and pancreas. The increased magnitude of the procedure has a significant effect on cardiac function after removal from the donor. Furthermore, we are utilizing older donors and those with circulatory diseases such as hypertension that we do not exclude now because of our donor organ shortage. A donor organ or a donor-recipient size mismatch or acute rejection may also complicate organ recovery. Of course, the ubiquitous acts of God that we all have to deal with at times occur.

Our experience with donor hearts that have failed consisted of 11 patients aged 19 to 63 years with a donor age of 23 to 47 years [8]. The ischemic time was 76 to 255 minutes. The devices used included the Symbion J-7-70 device (1), right VAD (3), left VAD (2), biventricular assist devices (4), and the intraaortic balloon pump (1). I should note all the patients who had VADs put in had balloon pumps as well, and 2 patients had multiple devices. In these 11 patients there were three deaths. The first death occurred in a patient who had cardiac arrest the day after the right VAD was removed, and I suspect there was ongoing right heart failure, but we did not have the use of a transesophageal echocardiogram then that we would now use to inspect the cardiac function before removal. The last patient was weaned from the device but had a stroke during the transplant procedure. The third death occurred in the operating room because we were not able to support the patient effectively. It is of note, however, that all but one of those hearts recovered.

The patients who survived are currently all long-term survivors and are in functional class I. In the patient who we were unable to support, postmortem examination revealed an anatomic abnormality of a super dominant right coronary artery, a diminutive left coronary artery, and an ostial lesion of the right coronary artery in this 36-year-old man. We believe he had a huge biventricular infarction at the time of organ retrieval.

We can, therefore, support such patients after trans-

plantation and can support them quite well. Also, we can expect recovery of the heart with appropriate application of support, which I believe should be early. We have tried to learn some things from this experience, and though I agree with Dr Farrar's patient selection hypothesis, in this group the patients are generally well selected and probably stress should be placed on early utilization, early utilization, early utilization. We limit the use of inotropic medications after transplantation to standard isoproterenol and low-dose dopamine. Occasionally we will add epinephrine, but if we have to go to more than 2 $\mu\text{g}/\text{min}$, depending on patient size, we will quickly look to a balloon pump and possibly get things in place for a VAD. It is important to eliminate distention injury in the transplanted heart. The acutely denervated heart loses a number of protective intrinsic reflexes, which can lead to more extensive damage in these hearts if distention occurs. We initiate right support earlier than left support because the danger in the right ventricle seems to occur early and the recovery of the right ventricle seems to take longer, as evidenced in the support of patients who required a right VAD for 7, 10, and 14 days as opposed to patients with left ventricular support, who recovered within 2 to 3 or 4 days. We have only had to use univentricular support in most patients; however, 2 patients had biventricular support, both of whom had serious ischemic injuries of the heart due to very difficult implantations after Jarvik removal.

Complete drainage of the affected ventricle is important. We only use as much inotropic support as is required to affect the working ventricle after VAD implantation. The VAD lines exit through separate incisions. The outflow line is placed in the superior pulmonary vein on the right using a 26F angled catheter that allows 5 L/min of flow, and the inflow cannula is placed in the ascending aorta under the sternum so that a tangential trajectory is achieved, assisting in obtaining hemostasis. The sternal incision is used in standard fashion, which allows these patients to wake up and be extubated in the postoperative period. We follow up the return of ventricular function by loading the ventricle while observing the transesophageal echocardiogram, a useful tool in the timing of weaning and removal of a device, and we do not use heparin except in the case of a total artificial heart or in our centrifugal VADs when the flow is less than 2 L/min. At 1 to 2 L/min flow the activated coagulation time is kept greater than 180 seconds, and at less than 1 L, greater than 300 seconds.

In summary, the patients are selected after transplantation. Most of them are good candidates for support, and we believe that if support is initiated early enough with the proper devices going from the simplest to the more complicated, good long-term survival can be effected.

MODERATOR PENNINGTON: Well, we all struggle with the question of whether or not we should proceed with our pharmacological agents to try to support patients in either category of postcardiotomy or bridging to transplantation, or whether we should go ahead and use mechanical devices. There are some differences of opin-

ion, and Daniel Loisanse has thought about this a great deal, has written about it and we are delighted to have him give us his opinions.

DR LOISANCE: Thank you, Dr Pennington. It is a real pleasure to fly from Paris to the California vineyards and discuss with you the issue of patient selection and what we try to do in Paris. What we try to do is to use a very flexible strategy, providing patient support with enoximone, which at the same time would permit us to avoid the rising cost of health care [9]. In this strategy, we initially use medical therapy; if the patient is responsive, he or she is bridged pharmacologically to the transplantation. If the patient is not responsive to enoximone, mechanical bridging is immediately undertaken. Should a patient's condition deteriorate on the pharmacological bridge, the patient will immediately be switched to the mechanical bridge.

Our experience is now based on 52 patients and all have been referred for transplantation or immediate mechanical bridge. All were unresponsive to maximal therapy including in a few patients intraaortic balloon pumping. All these patients had good indications for transplantation, and 4 were in deteriorating condition while on the waiting list. Most of our cases were acute, arising from a very recent history of ischemic cardiomyopathy or idiopathic cardiomyopathy. Fifteen of these patients had recent acute myocardial infarction. Only 8 patients were unresponsive to enoximone pharmacological support, and they underwent immediate transplantation. In 44 patients, the improvement was such that it was possible to gain time to restart the evaluation process and to either reconfirm the indication for transplantation or even find some contraindication to this transplantation. Twenty-six patients of the whole group of 52 were reconfirmed as good candidates. At 1 month 23 patients were living after either a mechanical bridge or a pharmacological bridge. Eight patients were still waiting for transplantation, most in stable condition at home. Eight patients had a contraindication to transplantation. They are living at home, in stable condition. At 1-year follow-up 20 patients were still living and 14 have undergone transplantation; 4 with a contraindication are still living and 2, who were sent to us for cardiac replacement, have been removed from the transplant list because of a recovery of myocardial function.

The most important reason for this strategy is cost savings. Forty-three devices costing approximately \$2.3 million US dollars were not used. We also better utilize organ grafts, which are used for patients with true indications for transplantation. In other words, we are trying to combine the patient's interest, which is obviously to stay alive, and the social concern, which is to avoid excessive rising costs in health care. There is obviously a black side to the picture. The concerns about this strategy are related to both the nonresponsive patients and the responsive patients. In the nonresponsive patients, what we may see is some form of super-maximal vasodilator action leading to prolonged organ dysfunction and to a delayed decision for implantation. This obviously in-

creases the risk to the patient for a device, the loss of vascular tone leading to the risk of irreversible failure of other organ systems and, finally, to a reduction in the transplantability of the patient on a device. The second concern is about the patients who are responsive to enoximone. They are living because of a major hemodynamic improvement, but they are at risk of sudden death, which may occur while they are still in the intensive care unit. We had 4 such patient deaths. Patients also have a sudden death risk after hospital discharge when they are in otherwise stable condition at home waiting on the list. We have lost 2 such patients. In other words, there is a 23% rate of sudden death among the population of patients who are ideal candidates for transplantation and who were in otherwise stable condition. This is quite unacceptable if we recall that this therapy was successful to resuscitate the patient in terminal condition. A second concern in this group of patients who are dramatically improved from a hemodynamic point of view is the incompleteness of the recovery process. When they are in the intensive care unit they are bedridden, and when they are at home they do not exercise as they should. So we do not achieve an ideal quality of life. This leads to the conclusion that we should not ask too much, but we should be reminded that this strategy is definitely a major help in the selection process of our patients.

MODERATOR PENNINGTON: Thank you very much, Dr Loisanse. I am sure many of you have comments or questions, and we want to entertain those. While you are thinking and getting ready to come to the microphone I will ask a couple of questions. Doctor Loisanse, we do not have enoximone but we do have dopamine, dobutamine, isoproterenol, and epinephrine, among other drugs. Do your patients receive any conventional drugs before enoximone or do they just go right to enoximone?

DR LOISANCE: All of these patients are first treated with dobutamine, dopamine, norepinephrine, all these cocktails. And if this does not work we add enoximone to the previous medical therapy. So, it is not a substitution but an addition.

MODERATOR PENNINGTON: I think we stated in our own experience that those patients with ventricular assist devices before transplantation did much better than those supported with drugs or intraaortic balloon pumps before transplantation [2]. Was there a difference in your two groups in terms of their survival or outcome after transplantation?

DR LOISANCE: No, the risk of transplantation is about the same.

MODERATOR PENNINGTON: I see, so it does not make much difference whether they got there by way of a mechanical device or drugs. Is that right?

DR LOISANCE: Correct.

MODERATOR PENNINGTON: Are there questions from the audience?

MR BRUCE SHOOK (Danvers, MA): I have a question for David Farrar. You presented some interesting data that would appear to be predictors of success, BUN for example, and I wondered if you could tell us whether you identified anything else that was statistically meaningful in the course of your analysis.

DR FARRAR: Actually those parameters that I presented were the ones that were significant. All had *p* values less than 0.05. Blood urea nitrogen was highly significant; creatinine was not. Previous operation and the interaction between age and sex were important. Older females did much worse than the younger males.

MODERATOR PENNINGTON: I think what we are being asked to do by the FDA, at least in this country, is to define precisely which patients we are evaluating in terms of those requiring mechanical support. And I think the data that Dr Loisanse presented and the data we are trying to generate at St. Louis University attempt to do that. For example, we have established a set of criteria based on drug dosages: 10 μ g of dobutamine, 10 μ g of dopamine, various limits of epinephrine and isoproterenol. Once we get beyond those limits, then the patient's chance is better to have a mechanical device than it is to continue on pharmacological support. And as much as we dislike that sort of "cookbook" criteria, we are being asked to develop such criteria to defend our practices.

DR GEORGE J. MAGOVERN, JR (Pittsburgh, PA): I wanted to ask Dr Emery what his experience has been with treating patients who have acute right heart failure after transplantation with right ventricular assist, and how successful that program has been in having those patients reverse their failure.

DR EMERY: You mean right ventricular assist alone?

DR MAGOVERN: Right or biventricular assist.

DR EMERY: I think that we have four biventricular assist devices and three right VADs alone. We do try to use only univentricular assistance, but, as I mentioned, 2 of the patients with biventricular assist devices had global ischemic injury with difficult implantations after bridging. The patients with right VADs were all able to be weaned. The first patient died, I think because we did not wait long enough and support him long enough for ventricular recovery. He went on the device because there was prolonged organ ischemic time and particularly high pulmonary vascular resistance in the range of 6 Wood units at the time of transplantation. We have been able to get all the right ventricular assist patients off the device, but there have only been three used. We do try to put the balloon pump in very early. And that has impressed me as helping people who might have right ventricular dysfunction by decreasing the afterload of the right heart by

unloading the left. I really think that early intervention on the right side is particularly important because when the right ventricle gets stretched, particularly if it has to recover against a relatively high afterload after transplantation, recovery takes a long time.

DR TIMOTHY B. ICENOGLE (Spokane, WA): It is not infrequent that pleas or cries for help come to centers that have such devices. Given the hypothetical situation of a call from a center across town where there is a 40-year-old person who has had a catheterization laboratory crash and operation and now is on biventricular assist but awake and making urine, would any of the panelists consider that patient as a candidate for a pulsatile assist device?

MODERATOR PENNINGTON: Well let me just answer that in our own center we have had several cross-city transfers. Actually we have received patients on centrifugal pumps. And we just believe that is a reasonable thing to do because it is not possible that every cardiac center become a transplant center. Therefore, that makes it incumbent upon the transplant centers to try to take care of this population of patients. Unfortunately I have to report that none of our transfer patients have made it to transplantation. Do you accept patients from outside, Dr Emery?

DR EMERY: We have tried not to.

MODERATOR PENNINGTON: Doctor Pae?

DR PAE: We do, but we have basically had the same experience as you. We have been unsuccessful.

MODERATOR PENNINGTON: Doctor Loisanse?

DR LOISANCE: We are a referral center, so we cannot avoid taking care of these patients. We have to take them.

MODERATOR PENNINGTON: Even if they are on a balloon pump or some other type of device?

DR LOISANCE: Yes, that is exactly the kind of patient that we are referred the most.

MODERATOR PENNINGTON: And . . .

DR LOISANCE: We do but the results are quite bad also.

DR ERIC A. ROSE (New York, NY): I would like to ask Dr Loisanse about the patients who are switched from intravenous to oral enoximone. In those patients do you use angiotensin-converting enzyme inhibitors as well or preferentially? Enoximone in this country in the class IV heart failure trials has actually shown increased patient mortality. Arnold Katz said at the American Heart Association meeting that the drug allows the patient to burn brightly briefly, which I think is an apt description of what

is allowed to happen. The one drug that has shown an effect on mortality in class IV heart failure has been the angiotensin-converting enzyme inhibitors.

DR LOISANCE: You are completely right. Now, a patient is not kept on enoximone for a long period of time. If they are in stable condition at home the major treatment is angiotensin-converting enzyme inhibition.

DR FRANCIS WELLS (Cambridge, England): Doctor Pennington, I would very much appreciate some clarification. Doctor Farrar showed very nicely that he had achieved an 11% mortality after transplantation with patients that he bridged. He also showed 35% mortality before transplantation, if I understand you correctly, in patients who were bridged; this gave a total mortality of 46% in patients going through to transplantation, and that is not quite the good results that perhaps some of us are beginning to think can be expected after bridging. I would very much appreciate clarification, if you could tell me the overall mortality for patients bridged.

MODERATOR PENNINGTON: Doctor Farrar, do you want to answer that?

DR FARRAR: You are absolutely right. The overall survival rate is about 54%, which takes into consideration the pretransplantation and the posttransplantation survival. If you look at all of the centers that are using our device, it is just about the same at every center. And that is something that we found fairly interesting.

MODERATOR PENNINGTON: Well, I think this is a very important observation of course, and one that we have tried to emphasize. In fact, when we use a device to try to bridge a patient we tell the patient and the family that the chance of getting a transplant is about 50%, and that they must be prepared for the possibility of failure before we put the device in. If renal failure or an infection develops then we have to take the device out or the patient has to die with it in, but transplantation is not considered. That is a very important part of the process. Our rationale is that we would rather expend the pump than a donor heart.

SPEAKER: Actually, 65% of patients achieve transplantation. Once transplantation occurs, the posttransplantation survival is identical to that of patients who did not require mechanical circulatory support.

SPEAKER: This is an important thing to keep in mind when you are comparing with Dr Loisan's figures.

MODERATOR PENNINGTON: Absolutely.

DR JOHN WOODARD (Oakland, CA): I would just like to ask Dr Farrar if he would care to comment on the previous cardiac operation as a risk factor. Is it the excessive dissection time or is it right ventricular failure? Have you got any mechanism for that?

DR FARRAR: Only 20% of the patients have had prior operations. We have not been able to identify any particular factor. We have looked at infection and bleeding, and they do not seem to be factors. But there is nothing we have seen.

MODERATOR PENNINGTON: I might just mention that in our experience at St. Louis University the fact that a patient had a reoperation is not a factor in terms of survival, either for postcardiotomy or bridging [1, 10].

DR DAVID J. COHEN (San Antonio, TX): This question is for Dr Farrar. You showed the survival difference between male and female patients to be very significant. Is this a question of size?

DR FARRAR: No. As a matter of fact, size and body surface area were not significant. Nor were they significant in relation to the female gender.

DR COHEN: So are there other reasons?

DR FARRAR: No. I do not have an explanation except that my understanding is that in other types of cardiac surgery female patients have a higher risk. Certainly it is even more apparent in these data. Only 20% of the patients are female, so there are only about 25 patients and maybe only 10 of them older than 42 years, so these are small numbers.

DR ROLAND HETZER (Berlin, Germany): I think this was a very interesting discussion. I would like to add a few comments from our experience with 63 transplant procedures to date with an assist device very similar to the Thoratec device. In addition to the risk factors that David Farrar has shown, we have seen that patients who had pneumonia before installation of the assist system and those who had spontaneous coagulation disorders before implantation certainly had a higher risk of failure during the procedure. I assume that you mostly excluded such patients from implantation, and we certainly would be very cautious in accepting those patients in the future. Also, I would like to comment on Dr Loisan's experience with enoximone. We have close to a 200-patient experience with enoximone in patients who were referred for transplantation, and only about 60% of the patients responded well to enoximone. The others either did not respond at all or had a short recovery and then went into cardiopulmonary shock again. I would not be so extremely enthusiastic about enoximone alone, and I think you almost always should be prepared to go to a mechanical device. Also, I would like to ask a question concerning assistance after cardiomy. I think to save assist devices one should probably go to a staged procedure. That means first use a centrifugal pump. If the patient after 48 hours would be a transplant candidate or shows signs of recovery, then we would probably go to a pulsatile assist device.

MODERATOR PENNINGTON: Unfortunately, we are just about out of time. I do want to say although we did

not cover the whole topic of the postcardiotomy patient, I know we will hear more about that as the session goes on.

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Panel II

Anticoagulation

Moderator: Jack G. Copeland III, MD

Panelists: O. H. Frazier, MD, Lawrence R. McBride, MD, Marko I. Turina, MD, and Christian Cabrol, MD

MODERATOR COPELAND: I think that we cannot really discuss anticoagulation without discussing hemostasis and bleeding with circulatory support devices. I would like to make a few comments before we proceed with our panel members. One thing we know for sure about our experiences with these devices is that the device interface with blood provides a constant source of stimulation of the platelet system and the clotting system. Sites of thrombus formation that have been reported include inlet and outlet cannulas, valves and valve mounts, housings, diaphragms, and the like. We have looked at platelet metabolism and found that platelets are continuously activated, presumably by their contact with the device. And if one looks serially at the β -thromboglobulin level, it is elevated. There is a continuous stimulation of fibrin metabolism. There is fibrin formation indicated by the persistent evaluation of fibrinopeptide A. Evidence of fibrinolysis in the form of XDP or cross-linked fibrin degradation products is also present.

Prevention of thrombus formation remains a problem. In 1985 we reported valve mount crevice thrombus in the Jarvik total artificial heart, and we have also seen small foci of platelet aggregations on a housing of biventricular assist devices. We use a fairly standard anticoagulation regimen for the total artificial heart, biventricular assist devices, and the Novacor left ventricular assist system. On the first postoperative day we start administration of dextran 40 at 25 mL/h and we give dipyridamole, 75 to 100 mg every 6 hours through the nasogastric tube or orally. Starting on the second postoperative day we begin administration of heparin and we maintain a partial thromboplastin time of 50 ± 10 seconds and continue the dipyridamole. By about the fifth to seventh postoperative day we switch from continuous heparin infusion to warfarin sodium, and we maintain a prothrombin time of about 18 ± 2 seconds. We continue dipyridamole administration. Any patient who has an episode that might be interpreted as a neurologic problem, for instance a transient ischemic attack, receives aspirin, 325 mg per day.

Finally, I would like to mention hemorrhage. We pre-clot the inflow and outflow grafts three times before heparinization. This takes about 20 to 30 minutes. Then we spray the outside of these grafts with biologic glue. Since doing that we have not had any serious graft hemorrhage. Before the use of this technique we commonly observed hemorrhage through the interstices of

the outflow (high pressure) graft. Thus, anticoagulation problems that I hope we will discuss today include hemorrhage, one of the major problems with each device. I think it is common, and seen in up to 30% of implants. It is often massive, resulting in tamponade. Tamponade may also occur late, weeks after implantation. I hope we will also focus on thromboembolism. If one looks, for instance, at the total artificial heart data, less than 10% of patients have embolic neurologic events and 5% have strokes with permanent neurologic damage. This may be less thromboembolism than we feared 5 years ago, but clearly there is room for improvement. To lead off I would like to ask Dr Frazier to talk. His experience has been primarily with the TCI device.

DR FRAZIER: The main problem in research in this area is the blood-biomaterial interface. We have to be concerned about that interface with any of this technology. The TCI device is designed to be minimally thrombogenic, so we have never been forced to deal with problems of clotting as much as bleeding. Bleeding has been a much greater problem than thrombus formation. Of course we completely reverse the protamine at the close of the operation, and we give no anticoagulant until the patient's condition is stabilized in the intensive care unit. At a convenient point we then start the patient on low molecular weight dextran, which is what we also use for intraaortic balloon pumps. And when the patient is taking oral feedings we start administration of dipyridamole and a low dose of acetylsalicylic acid. We really do not use heparin in the postoperative period unless the pump stroke volume becomes very low.

The lining of this pump housing is titanium microspheres. The pumping diaphragm, however, is an integrally textured polyurethane surface, which allows blood elements to catch very early on this lining. On a diaphragm taken from a 41-day patient, cells are present on the surface of the pump housing and pumping diaphragm. In a patient who has had the pump in place more than 200 days we have seen a very smooth surface with no calcification and with some endothelial cells on the surface. As far as I know, that is the first demonstration of endothelial cells cultured from an artificial surface in humans. As you know it has previously been achieved in pigs and dogs, but not in humans. These cells must be coming from the circulating blood cells.

A great advantage of this pump to date is that in more than 6 years of total use we have had only one episode of thromboembolic problems. That problem was that the

inflow cannula was kinked, leading to a distortion of the diastolic blood flow and a thromboembolic event at a little more than 100 days. But I feel very safe with this low level of anticoagulation with this regimen. We have done away with the blood-biomaterial interface.

MODERATOR COPELAND: Next we have Lawrence McBride from St. Louis University, who is going to tell us about their experience with anticoagulation.

DR McBRIDE: At St. Louis University we have used three different types of pulsatile ventricular assist devices: the Thoratec pump, the Novacor and Jarvik artificial heart. Our anticoagulation regimen in all these patients consists of starting them on dextran at 25 mL/h as soon as their chest tube drainage falls to less than 100 mL/h for 3 consecutive hours. In the interim we try to correct any coagulation abnormalities by infusing fresh frozen plasma as well as platelets as necessary. Once the coagulation parameters have been normalized, we start the patients on intravenous heparin at $10 \text{ U} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ and we adjust the dose to maintain a partial thromboplastin time of $1\frac{1}{2}$ times normal. When the patients are extubated, and they start on oral intake, warfarin sodium is added and we attempt to achieve a prothrombin time of $1\frac{1}{2}$ times the normal. We do not wean the heparin until the prothrombin time is $1\frac{1}{2}$ times control, what we consider to be the therapeutic range. We add aspirin, 75 mg per day, only if the patient has had a thromboembolic event, or we believe that the patient is at high risk for this, such as an individual who was supported with a device who also may have a prosthetic valve in place.

As we have heard throughout the morning, bleeding is a major problem in this group of patients. Of 80 patients who were supported with devices, 42 had the device inserted with the intent that their heart would recover, and 38 patients had the device inserted as a bridge to transplantation. As one would expect, the postcardiotomy group had more bleeding and required more blood products than the bridge to transplantation group. Blood losses at 48 hours were significantly different because of wide variance from the mean. Overall, 24 of our patients required reexploration. Over the last 40, however, only 8 patients have required reexploration as we have paid more attention to correcting any coagulation abnormalities and also we have improved our operative technique, especially with clotting the graft as Dr Copeland had mentioned. As one would expect, our survivors bled less than our nonsurvivors. However this was only statistically significant in the bridge to transplantation group. In our recovery group most of these patients died of myocardial failure with multiple organ failure.

Another major problem that these patients have is thrombus in the pump or systemic embolization. In our Thoratec group of 94 devices that were explanted we found evidence of either red cell or platelet thrombus in the system of 10 patients. Nine of these patients had predisposing factors. However, 4 of the patients had mechanical disruption of their flow for a period of time. Three of the patients had major gastrointestinal bleeding,

which required discontinuation of their anticoagulation for a few days, and 2 patients had severe septic episodes. In addition to this group we had 9 patients who had either clinical evidence or postmortem evidence of having a systemic embolization. We did not find any thrombi in the nine Novacor sacs that were removed. However, 1 of our patients did have a cerebral embolus several days after implantation. This patient had multiple organ failure, had a few episodes of sepsis, and also had a serious gastrointestinal bleed for which anticoagulation was discontinued.

Interestingly, 3 of these patients had pseudoneointimal formation in the conduit, a thin layer of collagen that lined the graft. It was adherent to the graft, and we are not aware of it having caused any problems for the patients. We had 2 patients who were supported with the Jarvik heart, and we found thrombus in one of these pumps. However, unfortunately both patients had clinical cerebral embolizations.

MODERATOR COPELAND: Our next speaker is going to deviate a little bit, I believe, from what you have heard from the last three. He is Dr Marko Turina from Zurich, Switzerland, who has had extensive experience with the Carmeda process cardiopulmonary bypass, and he is going to tell us a little bit about that.

DR TURINA: I would like to tell you about the work we have been doing in Zurich and that has been taking place in Europe working with heparin attached to the parts of the pump oxygenator system and of the assist devices. There are numerous advantages if you are able to attach heparin reliably to the surfaces and not systemically heparinize the patient, or use less heparin. Of course during cardiopulmonary bypass it will reduce the blood loss. You will have less blood transfused; consequently, it will shorten the operating time. But the additional effect, which we do not know very much about, involves less complement activation and modifying immunologic response and having less anaphylactic reaction from the protamine, which can be a problem. Decreased stimulation from heparinized surfaces may decrease generation of free radicals, hemolysis, and the neutrophil activation.

We have been using in the last $3\frac{1}{2}$ years both ionic fixation and end-point fixation of heparin in the tubing and the Maxima Medtronic oxygenator with the Carmeda. We have also had coated surfaces in the Bio-Medicus pump. We have performed a prospective, randomized study which was conducted by Dr Franz Agasa, who has done most of this experimental work and has been in charge of the clinical evaluation of this work. We used the Carmeda system in a prospective, randomized way for coronary revascularization. We used the same oxygenator in both groups, giving the group with the low heparinization 100 U/kg and the full heparinization 300 U/kg. We maintained the activated clotting time during revascularization procedures of the low group greater than 180 seconds. We were not courageous enough to completely eliminate heparin. I think we will always need some heparin. In the other group the activated clotting time was

kept about 480 seconds. We were able to grossly reduce, in a statistically significant way, the loss of blood and the amount of blood transfused. Half of the patients did not need any transfusions whatsoever. So the first clinical trial has shown that blood loss can be reduced and less blood is transfused. This was significant. We found no other significant differences.

The second clinical trial used the Carmeda system devices on the roller pump and on the centrifugal pump for the resection of thoracic aortic aneurysms. Partial cardiopulmonary bypass has taken a lot of problems away when dealing with a big thoracic aneurysm, especially those extending below the diaphragm when you have to replace the whole aorta. This is our method of choice now. The only fatality that we had in this group was in a patient with a ruptured thoracic aneurysm, which are rather difficult to deal with as you all know. Of course there is a word of caution about using these heparin-coated devices, because you can generate excessive thrombogenicity, and there is a theoretical danger of the closure of the bypass grafts, especially thrombosis of the endarterectomized artery and maybe a thrombus in the mechanical valve prosthesis. We have not observed that, but there is probably a need for a minimal heparinization. We found that thrombosis in the perfusion system may occur with minimal heparinization, and therefore special techniques have to be used to keep the blood moving constantly in the perfusion system. With this technique we have found no evidence of the activation of coagulation cascade.

MODERATOR COPELAND: Finally, Dr Cabrol will give us his vast experience from La Pitié Hospital.

DR CABROL: In our hospital we are not fortunate enough to have a hematology unit. So we had to engage a colleague, Dr Szefer, who specialized in this work, and this appears to be quite satisfactory. So the total experience is now 58 patients and more than 1,000 patient-days; 1 patient has had more than 600 days on the Jarvik. As our moderator explained, the anticoagulation must prevent many problems that are shared by many devices: fibrinolysis, exacerbation of platelet function, and exaggerated coagulation. We have to stop the fibrinolysis to stabilize the blood and the functions and to balance the coagulations. Fibrinolysis is due to the transformation of plasminogen to plasmin and destruction of fibrinogen and fibrin. To measure the fibrinolysis we have some test of plasminogen and fibrin degradation products. We treat fibrinolysis using aprotinin, one million units in intravenous injection followed by a drip of 4,000 U/min.

The second problem is a strong and permanent activation of platelets. To measure this exaggerated platelet activation in vivo we use β -thromboglobulin, platelet factor IV, and platelet aggregation in vitro. We normalize platelet function using dipyridamole in big doses, 600 to 1,200 mg/day. When the platelet function is stabilized we use aspirin in very small doses, 50 to 100 mg a day.

The third problem is to reestablish the normal balance between thrombin formation and neutralization by an-

tithrombin. To correct this excess of thrombin we use heparin, 1,000 to 5,000 U/day. I must say we had no biological bleeding in that series. Of course we have some surgical but not biological; that was always controlled by the technique of our colleagues. Also we had only two thromboembolic events, both occurring in our patient who lived 600 days with the Jarvik. She had two small episodes of neurological troubles; they were very transient. Examination of the device after use showed absence of microscopic thrombi in high-risk sites like Dr Copeland said, especially around the valve, and absence of iatrogenic bleeding. Finally, the various alterations in platelet function and coagulation kinetics linked to total artificial heart implantation require permanent anticoagulation and antiaggregation as well as a suitable follow-up. The protocol must be able to explore all the systems involved to modulate treatments to individual needs.

MODERATOR COPELAND: We are open for questions.

DR D. GLENN PENNINGTON (St. Louis, MO): I would like to ask Marko Turina a question. Let me give you a situation where you, let us say, have a Bio-Medicus pump and the Carmeda-coated tubing with Carmeda-coated cannulas. You have that system ready and you put it in a patient for ventricular support. The question is as follows: How much anticoagulation would you think is necessary? Would you use none? Also, is it necessary to follow up antithrombin III levels? And if so, what are your limits? If the antithrombin III level falls below a certain level should we give heparin? What advice can you give us?

DR TURINA: I do not think that you can eliminate the use of heparin altogether, because there are the vagaries of the implantation and there are times when you are not circulating in your system. There is always the danger of thrombosis. You are also running, especially if the patient has been receiving aprotinin, through some periods when the patient is in a hypercoagulable state. So to answer it simply in a situation like this, yes. We would use the heparinization that is used in vascular surgery just as the minimum heparinization to prevent some of the possible complications. We do not have hard data to prove that, but in the animal experiments when we had been running some of these devices they have been observed without any heparin whatsoever. We observed microemboli, and that is one of the pieces of indirect evidence that some heparin should be used. Only the activated clotting time is monitored.

MODERATOR COPELAND: I would like to ask Dr Frazier a question. You said that bleeding seemed to be a problem. Is that bleeding device-related or is that related to technique? How would you go about minimizing the bleeding?

DR FRAZIER: Well, bleeding is a patient-related phenomenon. Actually, in the implantation of these devices

there is nothing intrinsically about their implantation that contributes a lot to bleeding. Obviously with the total artificial heart implantation there are long suture lines. With the left ventricular assist device, the Novacor and the Thermetics devices, the ventricular attachment is decompressed. There is no pressure. It is a low-pressure line and the aortic suture line is right in front of you. We use a woven graft and have never really had problems with the graft bleeding. So the bleeding that we have encountered has been from patients with advanced, long-standing heart failure or hepatic dysfunction; particularly more recently, patients on prolonged Inocor support with accompanying platelet dysfunction have just been a coagulation nightmare. And the bleeding is the problem, not clotting.

MODERATOR COPELAND: So you treat the coagulopathy?

DR FRAZIER: I do. I wish we had access to aprotinin because it does seem that it might help with these difficult patients.

MODERATOR COPELAND: Doctor McBride, you talked about pseudoneointima. How long had those grafts been implanted? Do you think that duration of implantation has something to do with the presence of pseudoneointima?

DR McBRIDE: The longest patient had it implanted for more than a year, and he had this fine membrane that lined the graft and was densely adherent to the graft, which did not cause a problem with the function of the device at all. The other 2 patients, if I am not mistaken, had the device in for more than a month.

DR MICHAEL ALIER (Houston, TX): I do not want to belabor a point, but what about heparin-induced thrombocytopenia in this whole group of patients who are intermittently on lots of heparin a long time?

MODERATOR COPELAND: In our own experience that is one of the reasons we try to get off. In addition, we have had trouble keeping patients even on continuous heparin infusions because of oscillation of partial thromboplastin times. That is why we tend to move on to warfarin sodium fairly quickly. Dr Cabrol, have you had any trouble with that? You keep your patients continuously on heparin for the entire time that they have the device in place. Do you ever see falls in platelet counts or do you have trouble with using heparin?

DR CABROL: Well, no. So far we do not have any problems. We use heparin intravenously for some days, and after that we use subcutaneous heparin.

Panel III

Infections—Prophylaxis and Treatment

Moderator: J. Donald Hill, MD

Panelists: Bartley P. Griffith, MD, Marco Meli, MD, and Paul Didisheim, MD

MODERATOR HILL: We have heard throughout the day the problems associated with various cardiac assist-related complications. Infection, along with multiorgan failure and bleeding, is certainly one of the major complications to contend with once a device has been implanted. Physicians have struggled with infection for hundreds of years. Our ability to treat infection has steadily improved, but it remains a struggle in certain clinical settings. Patients who receive cardiac device implants are particularly vulnerable to infection. Often they have undergone multiple, lengthy surgical procedures with extracorporeal circulation, which has a specific immunosuppressant effect. These patients come to operation with a poor cardiac output, are usually nutritionally depressed, and have tissue edema and often anemia. They then receive a foreign body implant, which involves blood transfusions. This set of medical circumstances markedly increases the likelihood of infection. We have learned that antibiotics alone are not the answer. Today, we are going to hear three reports on infection followed by a question period to try and get a sense of how we can improve the management of these patients. First, Dr Bartley Griffith, of the University of Pittsburgh, will report on their experience.

DR GRIFFITH: The problem of infection with cardiac assist devices is an interesting one, and I believe, from the Pittsburgh perspective at least, that our ability to deal with infection in this setting has improved. The improvement has occurred in part because our focus on the device has changed. Over the last few years we converted from using the biventricular Symbion total heart device to predominantly using the Novacor ventricular assist device. The change occurred on the heels of 3 to 4 years of experience with patient selection and antibiotic protocols with the Symbion heart. We experienced a high infection rate with a high mortality rate in our Symbion experience of 21 patients. Our subsequent experience with the Novacor device and change in patient selection criteria has demonstrated that the lethality of those infections has decreased and almost disappeared. This happened at a time when the Symbion duration of support was only an average of 11 days. The average implant time of the Novacor device is now in excess of 60 days.

Clearly our perspective on patient selection has changed, an example of which is a patient who was sent to us from George Magovern. The patient came to us having been on Bio-Medicus pumps, and we implanted a

Jarvik total artificial heart. It was apparent that this patient was at great risk for development of complications. Youthful enthusiasm and zeal to help this patient, who had no other opportunities for treatment, were well placed. As it turned out the patient did very well and did not get an infection, but others like him have ended up on the other end of that survival scale.

I think it is important to point out that all patients with mechanical devices tethered by percutaneous leads have problems. These patients represent a nosocomial milieu who usually are in the hospital for more than 30 days. They are kept in a recumbent position for more than 10 days; some have intraaortic balloon pumps placed, and most are intubated and have intravascular lines placed with poor pulmonary mechanics and pneumonia of a clinical or subclinical level. This setting is ripe for bacteria to develop in the pericardial space that no longer has a muscle source for host defense (the heart) but an interposed plastic device. We know from studies in our laboratory and the work of others that the polyurethane material in the Jarvik device causes a respiratory burst in polymorphonuclear cells and leaves the patient defenseless against subsequent challenges. Perhaps the complications experienced by total artificial heart candidates present a degree of complexity not experienced by patients with heterotopic ventricular assist devices. Other centers that use the total artificial heart have had better experience than ours in terms of a low incidence of infection. Perhaps there is a common ground between our rather bad experience and the very good experiences.

Turning to our experience with the Novacor, the usual sites of infection are divided into the bloodstream, drive line, mediastinum, and the device. We categorize our incidence of infection into preimplantation, implantation, and posttransplantation incidence. Seven of the 24 patients in our Novacor series had a bloodstream infection. Two of these infections occurred during the preimplantation period and were treated with intravenous antibiotics. Two patients had *Candida*, 1 of whom was successfully treated with amphotericin. The second infection occurred in a patient who had been supported by the device for 287 days and ultimately died of a sepsis and an embolus. At explantation *Candida* vegetations were found in the Novacor device. Drive line infections were infrequent and were treated with local antibiotics interspersed with occasional intravenous antibiotics. The mediastinum, once a habitual source of problems in our experience with the total heart, is no longer a major concern. In 1 patient we successfully used muscle flaps in the posttransplantation period to manage mediastinitis. The posttransplantation

bloodstream infections were by and large innocent and related to intravenous lines and were easily treated.

Our antibiotic therapy has changed over time and currently includes vancomycin, gentamicin, and selective gastrointestinal decontamination. We do this to eliminate all but the anaerobic flora. This was prompted by reports from other major transplant centers who found benefit from gastrointestinal decontamination. We observed in our Jarvik experience that most of the organisms contaminating the mediastinum were enteric in origin. Selective gastrointestinal decontamination includes colistin, nystatin, and gentamicin. This is administered to intubated patients in an Orabase formulation coating the gums and the mouth or by nasogastric tube or mouth thereafter every 6 hours for 3 weeks and then every 12 hours until transplantation. Drive lines were not a problem in the Jarvik series due, I believe, to the short duration of support (11 days on average). Our longest implantation was only 54 days. The drive line in the Novacor device is usually very firmly adherent with strong tissue ingrowth to the abdominal wall. Upon removal of the device the part of the abdominal wall attached to the drive line comes out as well.

It is very important to have a well-healed insertion site. The patients who had difficulties with infection were individuals who had skin breakdown, either from an antibiotic reaction which caused severe dermatitis or irritation from a drive line that was pulling on tissue and caused the skin edge to bleed and crust. Our drive line dressing protocol is quite sophisticated. The nurses gown and glove and perform a very extensive preparation and cleaning of the surrounding area.

Getting away from prophylaxis, if treatment is necessary it is organism-specific and, as I mentioned, for drive line infections both local and intermittent systemic antibiotics are used.

I think that available treatment and experience has improved our ability to deal with infection. My comments about the Jarvik experience are not taken out of context. The Jarvik and Novacor were not synchronous series. What we learned from the Jarvik experience has been applied to our use of the heterotopic Novacor device.

MODERATOR HILL: Next we will hear about the European experience from Dr Marco Meli of Sion, Switzerland.

DR MELI: I would like to present to you a special problem concerning the relationship between infection and organ function. There is a clinical team at the Cardiovascular Institute in Lyon that participated in the implantation of the Thoratec ventricular assist device in 35 patients who were awaiting heart transplantation in 12 different European cardiac centers. Twenty-nine patients underwent transplantation, and 21 were discharged from the hospital. Eleven patients had infections during the circulatory support period and 6 patients were infected before. The goal of circulatory support is to provide sufficient cardiac output to support optimal organ function. To evaluate the impact of infection on the restoration

or maintenance of organ function we selected 24 patients. The criteria for inclusion in this study group was hemodynamic stability and a duration of support greater than 3 days. In 23 patients biventricular support was used; in 1 patient, left assist support alone. The antibiotic protocol used in most patients was third-generation cephalosporin for 48 hours if no infection was present before implantation. If the patient was infected before implantation the preoperative antibiotics were continued and only cultured organisms were treated. The criteria for sepsis was defined as the presence of at least four clinical signs of sepsis. For each organ/system (lung, kidney, liver, coagulation, gastrointestinal tract) we chose criteria for defining failure. Using the criteria we rated the patients according to the number of organs affected and their rate of recovery.

In the 24 patients screened in this study, 16 made a complete recovery and 8 patients did not. The difference between the groups was the presence of sepsis in the patients who did not recover.

The three most important laboratory parameters were platelets, bilirubin level, and creatinine level. Platelets in the septic patients stayed less than 100,000/ μ L. In the patients who were not septic the number of platelets increased after 1 week. The same was noted for bilirubin and creatinine levels. Bilirubin and creatinine levels stayed elevated in the septic patients and returned to normal values in the patients who were not.

In conclusion, the presence of the clinical signs of sepsis is associated with a poor prognosis for organ recovery. The presence of sepsis represents a contraindication that increases the risk of organ dysfunction.

MODERATOR HILL: Finally, to present a perspective on the future and how this problem is being investigated, Paul Didisheim of the National Heart, Lung, and Blood Institute in Bethesda.

DR DIDISHEIM: At the National Institutes of Health, we have made plans for research in this area. We are optimistic about a newly launched research program on the mechanisms of infections with implanted cardiovascular devices, which I would like to tell you about.

Federally funded research and development of circulatory support systems in the United States is administered by the Devices and Technology Branch of the National Heart, Lung and Blood Institute. This includes several different totally implantable artificial heart designs that are being developed and tested. In 1989 a proposal for setting aside funds for research on cardiovascular device-centered infections was discussed among our staff and with the advisory committees to our Institute. This proposal was approved and, jointly with the National Science Foundation, in the Fall of 1990 a request for applications for research grants in this area was announced. After review by a specially convened panel of non-National Institutes of Health experts, three proposals were funded in the summer of 1991. They are from Case Western Reserve University and the Universities of Alabama and Wisconsin. The three principal investigators are Drs

James Anderson, Magnus Hook, and Stuart Cooper. They have already met and begun to discuss collaborative projects. Briefly, the objectives of the three groups are as follows.

Jim Anderson's group will examine the role of bacterial adhesion and colonization on biomaterials, of absorption of specific plasma proteins to biomaterials, activation of leukocytes, specifically neutrophils and monocytes by the biomaterials and adhesion to them, and the physical and chemical properties of the biomaterials themselves. Conditions of the study will simulate the clinical situation by using human blood, physiological blood flow conditions, clinically relevant bacteria seen in device-centered infections, and clinically relevant biomaterials.

Bacteria do not adhere directly to a foreign surface; they bind to a protein coating on the surface. Magnus Hook and his colleagues propose to isolate and biochemically characterize the ligand binding sites on the proteins that mediate the adhesion of *Staphylococcus aureus* to biomaterials. These proteins are fibrinogen, fibronectin, vitronectin, collagen, and thrombospondin. The relative role of each of these proteins in bacterial adhesion to different biomaterials will be studied. They also propose to isolate and characterize the receptors on the bacteria which bind to protein ligands. The results of these experiments will be used to design peptides that could inhibit bacterial adhesion.

Stuart Cooper's group will assess, both in vitro and in a chronic canine ex vivo shunt model, staphylococcal and neutrophil adhesion and metabolism on a variety of polyurethane materials with varying surface chemistries. The aim will be to determine the influence on infectivity of certain surface properties such as surface free energy, surface charge, porosity, smoothness, and chemical composition and the role of various epitopes or regions of absorbed protein molecules. This study should improve our understanding of the relationship of infection to thrombosis in patients with cardiovascular devices.

There are other factors not addressed by these three projects that may play a role in device-related infections; many of these have already been discussed. They include the presence of bacteria on or in the device at the time of implantation, air-borne introduction of bacteria during the surgical procedure, spread of bacteria from preexisting sites in the patient to the implant, transcutaneous access lines, the nature of blood flow, especially stagnant and recirculatory zones within the device, and the nature of the anatomical fit of the device in relation to surrounding organs and tissues. Recent improvements in device design and technique have reduced the significance of these factors. In addition, these three newly funded projects and the collaborative efforts being initiated among them should provide useful new information about the mechanisms as well as the treatment of device-related infections.

MODERATOR HILL: We will now have the opportunity to have a discussion on cardiac device-related infection. But first I would like to ask a few pragmatic questions that come up frequently. First, Dr Griffith and Dr

Meli, in a routine bridge or postoperative recovery patient, do you use any isolation techniques? I am referring to anything that is different from routine open heart surgery.

DR GRIFFITH: No.

DR MELI: It depends. In half of the patients, yes; in the other half, no. In our collaborative study each center had a different technique. I have experience with both and found no difference in the incidence of infection.

MODERATOR HILL: I think the tendency is to move away from treating these people with any special isolation technique. In my center we do not use anything that is different from our normal routine.

Second question. In a postoperative patient who is doing well, when would you remove intravascular lines as they are probably the most common source of bacteremia?

DR GRIFFITH: Usually a day too late. I think, more often than not, we leave them in too long. Our intensivists enjoy having the mixed venous saturation and the cardiac output monitored with a Swan-Ganz catheter. It is always a fight with them. But I think when patients are extubated their lines should also come out. That usually is within the first week, which is probably safe.

MODERATOR HILL: Within 7 days in a stable patient?

DR GRIFFITH: Well, as soon as a patient is stable and extubated the lines should come out. In our experience that is generally more than just a day or two.

MODERATOR HILL: Doctor Meli?

DR MELI: It is important to reduce the number of invasive monitoring lines as quickly as possible. At the beginning one prefers to maintain patient monitoring. But I think now that I reduce very, very rapidly the monitoring lines in 2 to 4 days after hemodynamic stabilization.

MODERATOR HILL: That is an interesting range. In our center in a stable patient we would almost routinely try to remove all lines within 48 hours. If there are any significant secondary organ problems you are stuck with lines.

DR GRIFFITH: How do you administer heparin without a line?

MODERATOR HILL: We do it with a heparin lock, using bolus heparin every hour.

Now regarding the question of prophylactic antibiotics, do you use prophylactic antibiotics in routine open heart operations? I think probably the answer is yes. Do you alter your protocol in cardiac device cases? I am sure everybody starts them, but do you stop them? Doctor Griffith?

DR GRIFFITH: Yes. Our protocol for gentamicin and vancomycin is only about a 48-hour protocol. We continue selective gastrointestinal decontamination until the patient undergoes transplantation and thereafter for about 2 weeks.

MODERATOR HILL: How long does decontamination of the gastrointestinal tract go on?

DR GRIFFITH: For 2 weeks after transplantation.

MODERATOR HILL: So that could go on a long time?

DR GRIFFITH: Yes, the only thing that does not continue is the Orabase, which is the coating of the gum and tongue. That is discontinued when patients are extubated.

MODERATOR HILL: What type of monitoring for infection goes on during this period of time in terms of routine cultures, white blood cell count, temperature, and clinical observation?

DR GRIFFITH: I do not know that we have anything magic—we check all those things.

MODERATOR HILL: On a routine basis?

DR GRIFFITH: We do not routinely culture. We do not get a blood culture every week or a sputum culture every week. Only if there is a clinical reason to do so.

MODERATOR HILL: Doctor Meli?

DR MELI: I use prophylactic antibiotics for only 48 hours. I only use cephalosporin; no vancomycin, gentamicin, or other antibiotics. Concerning the decontamination of the gastrointestinal tract, I am not sure one can obtain complete sterilization of the gastrointestinal tract. Perhaps it would be dangerous to use in long-term patients. This type of decontamination may only be useful for intubated patients. After extubation I think it is not necessary to sterilize the bowel. It is very difficult to obtain a complete sterilization.

DR GRIFFITH: We do not want to sterilize it. It is aerobic free and fungal free, but anaerobic organisms are really encouraged.

MODERATOR HILL: In the last 3 or 4 years there has been a lot of speculation over the evidence of a relationship between infection and thromboembolism. Either of these complications can have a disastrous effect on a patient. I would like to present a scenario to Dr Didisheim for his response, but then I would also like to hear from Dr Griffith and Dr Meli.

In a patient with a cardiac device who has an infection (a pneumonia, urinary tract infection, or even a blood line infection), would you change the patient's anticoagulation regimen?

DR DIDISHEIM: There appears to be a synergism between infection and thromboembolism. A patient who has an infection is more likely to develop thromboembolism, but in this setting there is no experience to indicate that the level of anticoagulation should be changed.

MODERATOR HILL: Doctor Griffith?

DR GRIFFITH: Succinctly the answer is no. We do not change it because we try to ride the crest of the safe and unsafe level of anticoagulation. We use heparin early and then convert to warfarin at therapeutic levels. If I knew at what site in the coagulation cascade the infection was triggered, perhaps, with some of the newer agents we could target a specific area of the cascade to block or augment its defense. I suspect there are some people who have a better understanding of this than I.

MODERATOR HILL: Doctor Meli?

DR MELI: We have only had one thromboembolic event in our series. It is difficult to establish any relation between thromboembolism and infection. We had 11 patients who were infected during the implant period and who had no thromboembolic events.

MODERATOR HILL: I would like to encourage anyone who has a question to address the panel. In the meantime I have one other scenario that occasionally arises to pose to the panel.

You are 7 days into a cardiac bridge or recovery patient. *Candida* shows up in the urine in a completely asymptomatic patient. Would you treat or not treat asymptomatic *Candida* in the urine? Doctor Griffith?

DR GRIFFITH: It would depend on the colony count. Our tendency would be to treat it with irrigation for about a week and then reassess. Otherwise, if it were a very heavy growth and we were concerned about white cells and significant hypha forms, I think we would use amphotericin.

MODERATOR HILL: Doctor Meli?

DR MELI: I have had very negative experience with *Candida*. I lost 2 patients from *Candida* infections due to colonization of the cannula. For me the presence of *Candida* in the urine or blood is serious.

MODERATOR HILL: Doctor Didisheim, do you have any other comments on the infection and thromboembolism issue?

DR DIDISHEIM: I have been impressed that the one area we thought was going to pose the greatest risk of infection—tethered devices—has turned out not to have an increased risk. I would be curious to hear Dr Griffith's and Dr Meli's opinion on whether or not they consider patients with an external pump any more at risk for infection than those with an internal pump.

DR GRIFFITH: Experience has demonstrated that for the period of time the heterotopic paracorporeal ventricles have been used (ie, an average of maybe 30 days, at least in the Thoratec series) they seem to be very safe. I was surprised by that. Our initial preference was for a totally implantable artificial heart as opposed to a heterotopic device such as the Thoratec. Our experience has taught us differently. The problems we experienced with the drive lines have been exclusively in patients who seem to have some sort of skin breakdown at the drive line exit site—dermatitis in 1 and irritation from poor tethering in 2 patients. One patient had bleeding along the exit site from pulling of the cannula, which ultimately festered and had to be controlled with local and systemic antibiotics. I think the margin of safety is fairly broad, maybe up to a year in our experience and greater in other devices that have small exit sites so long as they are well secured with good tissue ingrowth.

MODERATOR HILL: Doctor Meli?

DR MELI: I have no experience with internal devices. Using external pump devices the incidence of infection around the cannula in our series is very low, only 1 case of infection around the cannula and absolutely no infection through the skin. The problem for an internal device is mediastinitis, which is a different problem. Mediastinitis is not a problem with the Thoratec external pump.

MODERATOR HILL: I see we have a question from the audience.

DR ROQUE PIFARRÉ (Maywood, IL): I would like to just put in a good word for the Jarvik total artificial heart. At Loyola University in Chicago, we have implanted 19 Jarvik total artificial hearts. Out of these we have performed transplantation in 17 patients. We have had no gross mediastinitis in our series. The short-term mortality was due to cerebral infarcts in 1 patient and acute rejection in another. The long-term mortality was due to pneumonia in 1 patient, sepsis in another, and chronic rejection in a third. We have had some superficial wound infections that were treated locally. We have had urinary tract infections and several pneumonias, but we have had no gross mediastinitis. I think that we need to underscore the fact that the total artificial heart, the Jarvik, is a good device and can still be used very safely.

MODERATOR HILL: Your results are outstanding and you are to be complimented on them. One of the things that I recall from an early publication of yours, when I think you had 14 patients, is that many of your implants were in postcardiotomy patients who had been referred for corrections and at the same operation had a total artificial heart implant. That is a very different population than patients with nosocomial infections, often in extremis and subjected to resuscitation heroics relative to the time of implantation. Can you update that for us today?

DR PIFARRÉ: Of the 19 patients we have treated, 8 had the implantation for the purpose of postcardiotomy failure and 11 implantations were for chronic cardiomyopathy and chronic failure.

Panel IV

Management of Secondary Organ Dysfunction

Moderator: William S. Pierce, MD

Panelists: James J. Hershon, MD, Robert L. Kormos, MD,
Walter P. Dembitsky, MD, and George Paul Noon, MD

MODERATOR PIERCE: The causes of secondary organ dysfunction are:

1. Device-related complications (eg, thromboembolism, hemolysis)
2. Improper support technique (eg, use of univentricular support when biventricular is needed)
3. Patient condition before initiation of circulatory support (eg, preexisting cardiogenic shock)

Device-related complications such as thromboembolism and hemolysis are gradually being overcome and generally do not represent a major cause of secondary organ dysfunction. The selection of an improper support technique, eg, the use of univentricular support when biventricular support is required, may result in a patient who has an inadequate cardiac output or a high central venous pressure. Renal failure or hepatic failure might develop in such a patient. These problems are preventable as we gain experience. Perhaps the most common cause of secondary organ dysfunction relates to the patient's condition before the initiation of circulatory support. In a patient who has had a previous cardiac operation and cannot be weaned from the heart-lung machine, there is often a period that lasts for an hour or more while different drugs and the intraaortic balloon pump are being employed. There may be inadequate support of the circulation during this period, and the manifestation of this problem may be secondary organ dysfunction.

A variety of complications can occur during ventricular assist pumping:

- Bleeding/disseminated intravascular coagulation
- Renal failure
- Biventricular failure
- Hemolysis
- Respiratory failure
- Thrombosis/embolus
- Cyanosis/patent foramen ovale
- Mechanical failure
- Cannula obstruction/low cardiac output
- Infection
- Perioperative infarction
- Neurologic

Bleeding is a common problem after device implantation. Renal failure may be caused by a low cardiac output before implantation of the device. Hemodialysis has been required in certain patients with ventricular assist devices, but the likelihood of a good outcome is significantly reduced. Some level of hemolysis is always associated with assist pumping but is rarely problematic. Respiratory failure is a common problem and results from a group of factors relating to a high left atrial pressure, sepsis, and other factors. Thromboembolic complications are not common and may not be pump related. For instance, a patient who has a prior myocardial infarction may have a thrombus adherent to the endocardial surface of the left ventricle. This material can be cast off as an embolus and cause serious secondary organ dysfunction. The problem of a patent foramen ovale in a patient who has a left ventricular assist pump in place is a serious one. With a high right atrial pressure, blood can shunt from right to left atrium across an otherwise insignificant patent foramen ovale and result in severe peripheral desaturation. Our group, Pennington's group in St. Louis, and Frazier and colleagues in Houston have all reported on this problem. Awareness of the problem and closure of the patent foramen ovale is indicated. Mechanical failures occur but they are fortunately very uncommon. Cannula obstruction problems frequently manifest themselves as low cardiac output. As we have seen in the pictures of the different ventricular assist devices, some groups have an entire series of cannulas that have slightly different angles and different tubing sizes. You can be certain that these different cannula designs came about because of problems of cannula obstruction that have occurred. Infection has been discussed in detail in an earlier section. Perioperative infarction may be a cause of thrombus formation in the natural ventricle and a cause of thromboemboli. Neurologic events are, of course, possible end results of thromboembolic problems or may relate to low cardiac output.

We have assembled a distinguished panel of speakers. Our first speaker is James Hershon from San Francisco. Doctor Hershon has been involved in the postoperative care of a number of patients with Thoratec devices.

DR HERSHON: I would like to tell you my conclusion right now is that you cannot make a silk purse out of a sow's ear. That is basically the theme here at the California Pacific Medical Center, formerly Pacific Presbyterian, formerly Pacific Medical Center. We use the Thoratec pump as the ventricular assist device bridge to transplan-

Table 1. Circulatory Support and Hemodialysis

Group	Total	Transplanted
Patients not requiring hemodialysis	113	83
Patients requiring hemodialysis	24	8

tation. And we have had about 21 patients with this indication. I have added a couple of patients to this series who actually had mixed devices, who came to us that way. Thirteen patients underwent transplantation; there were two late deaths in that group, not related to the bridge procedure. One was due to rejection and one was due to a stroke. There are 8 patients who died before transplantation or who just were never candidates for transplantation. Those are the patients we are going to talk about.

Of those patients, 4 died of multiorgan failure including renal, hepatic, and respiratory failure. One patient died of aspiration hypoxemia. The patient never left the operating room after implantation of the pumps. As it turned out, the patient had a very difficult intubation in the cardiac catheterization laboratory, where the patient crashed after cardiac catheterization. Two patients died of a combination of sepsis and emboli. Both these patients had previous devices, one being a Bio-Medicus device. The other patient was on extracorporeal membrane oxygenation (ECMO) for 12 hours. One patient who had a biventricular assist died as a result of a right ventricular assist device thrombus. This was a patient who had a very good native right ventricle and had good flow through the native ventricle with somewhat decreased flow through the pump, and I think that was the cause of the thrombus.

Focusing on the 4 patients with multiorgan failure, I think this was a failure of patient selection. We were somewhat enthusiastic about some of these patients. Three of them had preoperative evidence of multiorgan involvement. This is always a difficult problem when you have patients in acute congestive heart failure and cardiogenic shock; whether they are going to recover after you implant devices. A word of warning, and I would add a fourth item to Dr Pierce's list of causes of secondary organ dysfunction. Avoid any patient referred from the liver service. Two of our patients had initially been referred for liver transplantations. One of them turned out to be a patient with hemochromatosis who actually had severe congestive heart failure with what was described as only mild hepatic problems by our gastroenterologists. The other patient was referred for liver transplantation but actually, as his primary problem, had cardiomyopathy and had secondary congested liver but no actual liver disease. Multiorgan failure developed in a fourth patient while he was on assist devices. He did have some mild renal insufficiency preoperatively but no other organ involvement. As you can see, acute renal failure requiring hemodialysis changes your chances of being bridged to transplantation quite dramatically. Figures from the Thoratec series (courtesy of Dr David Farrar) show the follow-

ing (Table 1). Of 24 patients in that series, 8 patients actually made it to transplantation. Sixteen patients were not able to undergo transplantation. In patients who did not have renal failure, 83 of 113 patients underwent transplantation and only 30 patients were not able to undergo transplantation. So only 33% of patients with renal failure will make it, whereas if the patients do not have renal failure 73% will make it to transplantation.

In our experience, at least in a small series, when we did place ventricular assist devices in patients with evidence of renal and hepatic dysfunction they did not improve postoperatively even though we used biventricular assist. Right ventricular failure after implantation was not a factor, as far as we know, in these patients. Obviously there is an extremely high mortality, and I think the critical thing, which is not always easy, is the patient selection that is really going to determine your outcome.

The risk factors for multiorgan failure or death are not a surprise: ECMO or mixed devices; a long cardiopulmonary bypass time in postcardiotomy patients, which may lead to multiorgan failure and infections; previous operations or multiple operations in the same sitting; and prolonged low cardiac output syndrome. One of the patients who we had with multiorgan failure had very low output preoperatively. I think we were about a day late and a dollar short in getting devices into that patient; they probably should have been put in the day before. Again, I would emphasize that I think it is difficult to prognosticate preoperatively if you do have evidence of multiorgan involvement. However, I would stay away from anybody who has an elevated prothrombin time not due to warfarin anticoagulation.

MODERATOR PIERCE: Thank you very much, Dr Hershon. Our next speaker is Robert Kormos of Pittsburgh.

DR KORMOS: I agree with most of what you just heard. I only want to make several comments with respect to the issue of multiorgan failure. As in everything in nature, timing is the critical issue. I think we are not the only people who have to deal with this problem. Of 27 patients, we have had 8 people who died on the device. Of those 8, clearly 7 died with multiorgan failure. Of those 7, just to put it into perspective from Dr Pierce's list of causes, probably 3 of those patients died because of a combination of preexisting multiorgan failure and the fact that we may have delayed in the use of right ventricular support when it was indicated, which retrospectively is more clear now than it was then. The rest of those patients died with what I believe is a sepsis-related syndrome that preceded the implantation of the device. And I think patients with many of those factors you just heard Dr Hershon talk about, patients who, for example, are autoanticoagulated, are a very high-risk group of patients. Similarly, those patients who have fevers without positive blood cultures or have elevated or mildly elevated white blood cell counts with immature forms, bands in the white count differential, are very high-risk patients. And I think they represent patients with whom

the critical care physicians are very familiar, patients with what is called sepsis-related syndrome. Only 40% of those patients will have positive blood cultures. And so you may be somewhat falsely secure in putting devices in those patients because they will have persistent multiorgan failure, at least from what we have seen, after implantation of the device. That is exemplified by the fact that many of these patients died with multiorgan failure even though their cardiac outputs on biventricular support were in the range of 5 to 6 L/min. So it is not just a perfusion problem.

There are a couple other issues. Clearly the major organs that are involved here are liver, kidney, and lungs. We have seen adult respiratory distress syndrome (ARDS), very rarely, but it does exist. And ARDS usually is associated with some kind of septic syndrome. It may relate to drugs given before implantation. For example, ARDS has been found to develop very frequently after open heart operations in patients on amrinone. We have used ECMO in the setting of a Novacor left ventricular assist device in one situation. We cannulated the right atrium and returned the flow, via ECMO, to the left atrium. That patient did well and was discharged. I am not advocating that. That is a very complex type of support. Patients with bleeding and multiple transfusions may have development of ARDS and subsequent right ventricular failure. Renal and liver failure often go hand in hand. All I can tell you is that on circulatory support, it is extremely important to lower the central venous pressure. Very commonly, even on biventricular support, there is a tendency in intensive care units to volume load these patients because they often have capillary leak syndrome. The volume that you put in tends to build up in the periphery, and you see them trying to crank up the central venous pressure and keep the volume up. It is safer, and a little bit more tricky perhaps, to use specific α -adrenergic agents to keep the mean arterial pressure up in this setting. The only thing I want to mention is that in the setting of biventricular failure and multiorgan failure we have used various dialysis-type modes to reduce the volume of the patient when necessary. But our general feeling is that once you are in a situation of multiorgan failure on this type of support, it is usually a preterminal event.

MODERATOR PIERCE: Thank you very much, Dr Kormos. Our next panelist is Walter Dembitsky from San Diego. Doctor Dembitsky has had experience with the Symbion pumps, Thermedic pumps, Bio-Medicus, Hemo-pump, and Carmeda-coated ECMO circuitry.

DR DEMBITSKY: I think as our experience with devices increases and the quality of devices improves, we will be able to select patients earlier and earlier. Hopefully we can prevent some of the multiorgan systems failure that we are encountering as a major liability of all of these devices. The one thing I think that is important in our opinion is to maintain an adequate tissue perfusion gradient. By that I mean the difference between the mean arterial pressure and the central venous pressure, which

we like to see be around 40 mm Hg. I would like to also echo Dr Kormos' admonition to keep the central venous pressure low. When we started doing extracorporeal CO₂ removal for pulmonary failure, we noted that patients would come in with arterial pressures that were adequate but very high central venous pressures as a result of the high inspiratory ventilatory pressures. Almost immediately after these patients were taken off the ventilator they would begin on a brisk diuresis. This shows how effective lowering of venous pressure is on peripheral organ function like that of the kidney. The one thing that we have done recently with our patients in multisystem failure, as you have already "bought it" once you have it, is to try and deal with the oncotic pressure. We begin early continuous arteriovenous hemofiltration, and we augment the oncotic pressure by adding albumin to these patients, believing that most of them are hypoalbuminemic. Then we can enhance the recovery phase and diminish some of the ARDS that you encounter later. When we do have a patient with ARDS we also try to look for potential causes of that: factors that overwhelm the reticuloendothelial system and the liver such as abdominal sepsis. When a patient does have ARDS and meets ECMO criteria, we have been using extracorporeal CO₂ removal techniques using the Carmeda surface with some success. We try and diminish the pulmonary insult that you produce by treating ARDS with persistently high inspiratory pressures.

MODERATOR PIERCE: Thank you very much, Dr Dembitsky. Our final panelist is Dr George Noon from Baylor.

DR NOON: The best treatment for multiorgan failure is prevention. Oftentimes we are not lucky enough to be able to prevent it. But the next best thing is the early application of the device. Also of importance in the incidence of multiorgan failure is the type of device and the situation in which we apply it. For example, those patients who are treated with emergency cardiopulmonary bypass in the catheterization laboratory or in the intensive care units have much higher complication rates than patients in whom we electively put pumps, for example, a long-term device like the Novacor. In our use of centrifugal pumps and left and right ventricular assist devices in patients, we have had experience with 125 applications. There has been a very high incidence of problems in these patients.

The causes of death are related to ventricular failure, bleeding, encephalopathy, multiorgan failure, infection, respiratory failure, acute myocardial infarction, and severe cardiac graft rejection. There are many problems that occur in these patients. The complications that occurred in the patients although not causing death include bleeding, renal insufficiency, encephalopathy, infection, respiratory insufficiency, hemolysis, and thromboembolism. Most of these are not device-related complications. These are patient-related complications. If we were able to apply the devices sooner, before these problems occurred, we would see fewer of these complications. In the Novacor,

for example, we see very few of the complications that we see with the Bio-Medicus pump. The Novacor is put mainly in patients who are in more stable condition.

Supporting patients with short-term devices, such as cardiopulmonary bypass or the centrifugal pumps, does not provide time for the patient to heal multiorgan problems that develop. For example, in some patients with the Novacor, anywhere from 2 to 3 months may be required to overcome multiorgan failure. One patient who had some pulmonary problems (tracheostomy, ARDS) took a period of 90 days to clear up his lungs.

In the management of patients with secondary organ dysfunction, the main thing is to try and prevent it with early application of the assist device. Because these devices are fairly free of problems it is better to apply them early rather than later. It is important to maintain a cardiac index of $2.1 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ or more while the patient is being supported to minimize the pharmacologic support of inotropic and vasoactive agents, and to optimize fluid and electrolyte balance. As Dr Dembitsky indicated, we also like to maintain a colloid oncotic pressure within normal limits. This may take a lot of albumin. We like to minimize the fluid resuscitation, especially with crystalloid. These patients can come out of the operating room gaining 10 kg or more, because of long periods of resuscitation with crystalloid. They can also obtain a lot of free fluid just from transfusions. Most of the time diuresis alone is not enough to be able to handle this large extra load of fluid that these patients have. So we, like Dr Dembitsky, like to use the continuous arterial venous hemofiltration, starting in the operating room and carrying it out into the intensive care unit, to keep these patients with good oncotic pressures and keep them from getting so much third spacing. This has been very helpful in the treatment of these patients.

Another important thing is to be able to meet their nutritional needs. Support and treat the organ systems as indicated. Employ anticoagulation as indicated for the application of the device. Maintain a good cardiac output and appropriate fluid balance.

MODERATOR PIERCE: Thank you very much, Dr Noon. Are there questions for any of the panelists? Doctor Richenbacher.

DR WAYNE E. RICHENBACHER (Salt Lake City, UT): I have a question for Dr Kormos. You made the comment that in spite of the fact that some patients have a cardiac output of 5 or 6 L/min some patients will persist in the development of multisystem failure. In the last 2 or 3 years in the critical care literature, a great deal of time has been spent looking at oxygen delivery and arteriovenous oxygen differences and serum lactate levels. It is stated that some patients who have cardiac indices of 2.2 and $2.3 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ still may require a higher oxygen delivery. Perhaps we should make them hyperdynamic with cardiac indices much higher. What is your approach?

DR KORMOS: As we follow up the patients in the coronary care unit, one of the things we look at more and

more is the mixed venous oxygen saturation. Some of the patients who received implants had cardiac indices that were fairly high. As they were induced with anesthesia their cardiac indices were almost $3 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$. Yet those are the very patients who went on to have development of multiorgan failure. And when we looked at their mixed venous oxygen saturation in the critical care unit they were down around 30%, 27%, that sort of thing. So I think you are absolutely right. We are going to have to move to something like continuous oxygen saturation measurements more and more rather than just looking at simply the numbers, the cardiac index or output.

MODERATOR PIERCE: Doctor Hershon, can you comment on that question?

DR HERSHON: I am not sure that increasing assist pump flow will help you after multiorgan dysfunction has already developed, but it is an interesting concept. I do not know what other problems may arise by having much higher flows than what we normally use.

MODERATOR PIERCE: Thank you. Other questions or comments from the audience? Yes, Dr Pennington.

DR D. GLENN PENNINGTON (St Louis, MO): I wonder if you can give the criteria by which we would or would not use these systems. For example, above which creatinine level would you not use these systems? Above which creatinine level would you not implant a device? Above which bilirubin level would you say that it is too far gone?

MODERATOR PIERCE: Do you want to start it off, Dr Hershon?

DR HERSHON: I think it is very difficult to say that, as you probably know. But I think if the patient has a creatinine level greater than 2 mg/dL, I would be very concerned. And I would say this, if the prothrombin time is elevated greater than 14 seconds, I would be extremely concerned about putting devices in that patient.

DR PENNINGTON: How about bilirubin? Is that a factor?

DR HERSHON: I do not worry about bilirubin too much.

DR KORMOS: If the initial creatinine clearance is in the range of 25 or 35 mL/min, which it can be in some of these chronically ill patients, then I think if you see a creatinine increase from 2 to 3 mg/dL, that is an extremely bad situation. On the other hand if you have normal creatinine clearance and you see a creatinine bump from 2 to 3 mg/dL, the patient will tolerate that kind of insult. So that is why it is very difficult to set those limits. But I think, by and large, if we see creatinine levels in general greater than 3 mg/dL, I would be very concerned and I probably would try other forms of support to see if I could restore

renal function before I went on to one of these more complex devices. I think if the bilirubin level is greater than 4 mg/dL, 4 to 5 mg/dL, I am probably not going to put a device into a patient.

MODERATOR PIERCE: Doctor Dembitsky, would you comment?

DR DEMBITSKY: Well, I think it depends on whether the patient has chronic or acute disease. If the patient has chronic liver failure and then you are faced with a high bilirubin level, I think that is a contraindication probably in the long run. But in our experience we have put devices in successfully and had native heart recovery as well as successful bridge to transplantation with creatinine levels greater than 5 mg/dL and patients acutely ill, and bilirubin levels greater than 5 mg/dL. I think it depends individually on each patient. It is very difficult to select a single number.

MODERATOR PIERCE: I think that is a very important point. Doctor Noon?

DR NOON: We make the decision to implant a pump on an individual basis, carefully evaluating each patient. But in most patients with a creatinine level greater than 3 mg/dL we are very cautious about putting a device in.

MODERATOR PIERCE: Okay. Thank you very much. Doctor Wolner.

DR ERNST WOLNER (Vienna, Austria): I am a little bit surprised that none of the panelists has discussed the relation between multiorgan failure on one side and infection on the other. It seems, in our experience, when you have a proper functioning device and a good cardiac output, you can control renal failure. You can control some hepatic failure and also respiratory failure, as long as the patient does not have infection. When the patient has an infection, then usually multiorgan failure develops. My question is: In how many of your patients, Dr Noon, in whom you have observed multiorgan failure have you observed additional infection? In our experience, the main problem in multiorgan failure is the additional infection.

MODERATOR PIERCE: Thank you very much. Doctor Noon, do you want to comment on that?

DR NOON: I cannot give you the exact number, but I agree with you that most of the patients who do have multiorgan failure, because of such things as metabolic changes or lowered resistance, end up with infection. I am not sure whether infection is the cause of the multiorgan failure. I think it is the other way around.

MODERATOR PIERCE: Doctor Hershon? Comments?

DR HERSHON: I think that many of these patients ultimately die of infection because they have multiorgan failure. It is the same thing with people with ARDS, who do not die of respiratory failure, they die of something else, usually infection. Lactic acidosis develops in these patients, and they look septic near the end. We never culture anything out. They are on antibiotics and so on. They may well die of infection. But I think if they have multiorgan failure it is very difficult to reverse even with good cardiac outputs.

MODERATOR PIERCE: Okay. Thank you very much. Doctor Meli?

DR MARCO MELI (Sion, Switzerland): The relation between infection and multiorgan failure is fundamental. In our series we have obtained complete renal recovery with return to preoperative values of creatinine in patients without sepsis, without infection. But in patients with sepsis, this recovery is partial or not present. Patients have been maintained with hemodialysis for 3 weeks on assistance without increasing the morbidity and the mortality. In our experience, a value greater than 3 mg/dL for creatinine is not a contraindication.

MODERATOR PIERCE: All right. Thank you very much. Well, I think we are all in agreement that we would like to select our patients very carefully, implant the devices early, and hope that we can minimize the secondary organ dysfunction. I would like to thank the panelists for their very interesting contributions and the audience for their participation.

Panel V

Long-Term Biventricular Assist

Moderator: Charles-Julien Hahn, MD

Panelists: William S. Pierce, MD, Don B. Olsen, DVM, Kenneth Butler, and Robert T. V. Kung, PhD

DR PIERCE: I am going to discuss an electrically powered artificial heart that we have been working on for 8 years. It is placed in the chest in the orthotopic location, and the electric motor and motion translator, which is a device called a roller screw, is positioned between the two ventricles. These are pusher plate activated ventricles. We have to have all of the component parts that most of you are familiar with. Because this is a closed nonvented system, there has to be a compliance chamber in the left thorax. The electronic control system and emergency implanted battery system is placed in the subcutaneous position. And, of course, energy is transmitted with the wireless technique of inductive coupling with a primary and secondary coil and then an external battery pack. I think most of you are familiar with the overall design principle.

On cross section of the artificial heart, there is a pusher plate located at each end. There is a fixed distance between those pusher plates. In other words, they are attached but they are not attached to the blood sacs. The rotor of the motor is attached to the nut of the roller screw. As this motor rotates some four or five revolutions in one direction and then counter rotates, the pusher plate moves back and forth a distance of about 2.5 cm. The two main items of the prime mover and motion translation system are the brushless direct-current motor (Saracen) and the stainless steel roller screw (SKF transroll). These devices are widely used in the machine tool industry, and they are also a component of the wing flaps of the Concorde. Any of those of you who came to the meeting across the ocean in the Concorde, the SKF roller screws actuate the wing flaps on that plane.

Thus the components include the motor and motion translator, biomer polyurethane blood sac, and the polysulfone end caps, left and right. We use Björk-Shiley tilting-disc valves. The implanted batteries are designed to provide about 45 minutes of energy to the pump if the primary and secondary coils are separated. Because gases can diffuse in and out of the compliance chamber, we have to have some sort of a port through which we can access that compliance system and measure the gas pressure and change that pressure in accord with the needs of the device.

In the laboratory, the first designed pump that we worked on instead of using a roller screw motion trans-

lator used a drum cam having three cam followers. We had pretty good luck with 1 of those animals, but we had quite a bit of problem with the mechanics and with the little tiny cam followers. We subsequently abandoned that system and began to use the roller screw system. And we are starting to have a little better luck with our animals; 1 is still going and has passed the 11-month mark.

In the design of the animal experiments, we use closed systems. The pump is placed in the thorax as is the compliance chamber and battery pack, or we use an implanted battery and control system, the energy transfer system, a subcutaneous access port to get into the compliance chamber, and the external battery pack, or, of course, most of the time the animal is just kept on the house electrical supply.

At 200 days after implantation, the animal weighs about 103 kg and the pump handles about 10.5 L of blood per minute. The animal has a very low venous oxygen saturation as you might expect. But he still eats vigorously and actually looks pretty good. So we are very, very encouraged about this. This particular animal did not have the energy transfer with the coil arrangement, but the ones that we are doing now do have that system. So we are looking forward to doing an additional series of animals and see if we can continue the record of having animals that will last for a long time. Our next speaker is going to be Dr Don Olsen, and we will hold our questions until the end.

DR OLSEN: The University of Utah and Institute for Biomedical Engineering has been working on an electro-hydraulic artificial heart now for about 4 years. And in concept we have the following: internal batteries, internal electronics, and the TET telemetry coil system, with TET meaning transcutaneous energy transfer of power to the induction coil system. Our internal batteries are supplied by the consortium group between Ottawa Heart Institute and the University of Utah, and we are very pleased with that. The entire intrathoracic components all fit within the pericardial sac. We do not have a volume displacement or compliance chamber in our prototypes presently. We have always strived for simplicity and miniaturization. We have a titanium encasement. There is a brushless direct-current motor housed within this containment with the electrical pass through for back EMF control of the commutation. The axial flow pump reverses such that the hydraulic oil flows back and forth between the right and

left ventricle, coupling the right and left ventricle both volumetrically as well as in timed sequencing.

Our test model that we have been using in a series of acute calves is the Utah 100 type artificial heart. Actually this is an 80-ml stroke volume device. Today I would like to address how we achieve balance in this coupled system without external ports and without a volume displacement or a compliance chamber. We do that by making a small atrial septal defect here between the right atrial cuff and the left atrial cuff. This, then, is a small-diameter, and we will talk about that orifice that allows a volume of blood to move back and forth.

Our surgical procedure is the following. First we expose the natural heart, do our cannulation, and establish the cardiopulmonary bypass. Then we do the cardiectomy. We make sure of hemostasis then. We now are measuring through our heart-lung machine the systemic flow of the calf. But we are also able to measure the amount of bronchial flow return into the left atrium. We use this measurement in making a decision on which of the predesigned and prebuilt intraatrial septal orifices to use in these atrial cuffs. Then we go ahead and surgically implant the device and wean the calf from the cardiopulmonary bypass on to the electric powered artificial heart.

The purposes of the *in vivo* acute experiments were the following: to establish the intraatrial shunt performance, verifying that we can indeed achieve ventricular balance and that we maintain patency of that atrial shunt; to look at the hematological effects, hemolysis, and thrombus formation within the device and all of its components and attachments; and to examine the electrohydraulic TAH 20 system's performance both in regard to the fit anatomically and in regard to the physiological performance as far as adequate cardiac output is concerned.

In a series of 6 calves the measured bronchial blood flow as a percent of the flow of the cardiopulmonary bypass machine goes from a low of 5% to a high of 17%. We have learned that in those calves that exceed 12% we have a difficult time in establishing balance. The shunt size that we have selected to implant with each particular bronchial flow has been narrowed down to two sizes; we avoid putting the electrohydraulic artificial heart in a calf that has a high left-left shunt. During the course of the experiment we have measured the left atrial pressure and subtracted from that the right atrial pressure giving the change in pressure across this intraatrial shunt. We find that the highest we had was 6 to 10 mm Hg and the lowest we had was 2 to 5 mm Hg. In the longest living calf (about 9 days), the average difference between the mean left atrial pressure and the mean right atrial pressure was about 3.5 mm Hg, greater on the left than on the right. Occasionally we would have some spikes in pressure difference. Presently our motor speed control algorithm is being addressed to see if we can minimize these spikes, but they are relatively transient. Part of it I think might be a hammer effect from the method of open port measurements that we employ.

On the bench we tried to look at some of the flows using contrast media. This shows quite readily that we do

have that shunting. There is a higher shunt from left to right than the reverse. In the calf who lived 9 days the left atrium and the orifice of the small intraatrial shunt were quite clean.

The conclusions from these 20 *in vivo* experiments were the following: The intraatrial shunt provides adequate balance throughout a variety of bronchial blood flows. The intraatrial septal shunt has shown no evidence of thrombosis or occlusion, albeit so far our longest experiment was 9 days in these acute studies. The size constraints of the animal do exist and can affect the cardiac output and device performance even in our miniaturized system. Furthermore, we have had no evidence of intraventricular thrombosis formation except in one experiment where we had an electrical device failure and stoppage of the device without adequate heparinization. These experiments have been a great learning experience, resulting in 18 design changes. The system meets the physiological demands with its automatic control algorithm.

Now we have made a totally integrated device. This device is being built now for animal testing; it has an 80-mL stroke volume and will fit totally within the pericardial sac. Doing extensive fit trials we have successfully fit this clay model into a 57-kg and a 68-kg cadaver, although the 57-kg cadaver did have cardiomegaly. But it does fit well. We also have successfully fit the model with slight modification of the length and angulation of the inflow outflow ports into a 75-kg sheep and an 80-kg calf. This device will have an 80-mL effective stroke volume. Presently we are preparing for additional animal, cadaver, and human intraoperative fit trials.

MODERATOR HAHN: Thank you so much, Dr Don Olsen. Now I will ask Mr Ken Butler to give his lecture.

MR BUTLER: Indeed it is a pleasure for me to be here representing my colleagues at the Cleveland Clinic and my co-workers at Nimbus and present to you a run down of our particular artificial heart device that we have been working on for the last 4 years.

From the anatomical view, central is the blood pump energy converter unit that fits in the chest, replacing the natural heart. Our system is a dual pusher plate and it does have to have its compliance space managed; we do this with a flexing diaphragm chamber that is connected via a duct to the interspace. Gas is transferred back and forth between the interspace of hemodiaphragms and the flexing chamber, which faces into the lung space. We also have refill port that is accessed percutaneously.

The main power is derived from primary batteries that are located on the outside, and we also use a TET system including the secondary coil, which is implanted subcutaneously over the left chest. We are using the Thermedics or Thermocardiosystems version, and it has a secondary coil that fits on the outside over that. That transmits alternating current power across the skin, which is then conducted down to what we call a power module, which

is actually a rectifier that converts the current into direct-current power, which then drives the energy converter. The electronics package in our system is contained within the central blood pump and energy converter. An appendage is the internal battery, which is connected into the power module. The power module also serves as a connecting point for the various cables. So you can remove the internal battery and remove the secondary coil without disturbing the energy converter.

The blood pump itself is in the "human configuration" as a result of extensive anatomical studies conducted at the clinic, where every dimension was critically evaluated to make sure it would fit in a maximum number of adult patients.

The blood pump energy converter has been our main focus of work over the last several years. This is an entirely new design for us. Although we have had a considerable amount of experience with left ventricular assist systems using actuation and energy converter technology, this is really a new departure for us. The energy converter is contained within a titanium superstructure. The ventricles themselves are made of a carbon-impregnated epoxy, which has saved us a considerable amount of fabrication complexity, and they certainly are lighter than our titanium castings. There is a dual pusher plate. We simply rely on an alternate ejection from the left to the right. While the actuator is engaged in ejecting on the right side, the left side is free filling. The pusher plates, when they are filling, are disengaged from the sac or the rolling diaphragm. Conversely, on the right side when it is ejecting on the left it is filling on the right. So our control system essentially is to match our actuator cycling frequency with the fill rate of the blood pumps. If we go too slow we will impede filling. If we go too fast we will actually start an ejection while one of the ventricles is filling. So all we have to do is match our motor speed to the fill rate. And we do that electronically with a rather simple system, which I do not want to get into here.

The energy converter is based on an electric motor continuously driving a gear pump that puts out a flow of hydraulic fluid. That fluid cycles a piston back and forth in a container, which provides the actuation. We have a mainspring in the device that gives up force when it is ejecting on the left side and is cocked when the right side is ejecting. So it evens out our power distribution.

The diaphragms are the flexon rubber that the Clinic has been using for years. And we do use the biolyzed coatings that the Clinic has developed on all the blood contacting surfaces.

This is the book on our system as far as the key characteristics. I think all the systems are coming to about these weights and volumes. Our capacity is a 60-mL blood pump. It can generate up to roughly 10 L/min, 60 beats per minute. The direct-current power consumption at its maximum is 15 W. Our internal battery time, based on our latest tests, is in excess of 60 minutes, and that is at a 6 L/min condition; that is specified for the internal battery.

We have been concentrating the last few months on in

vivo tests, and I would like to focus the rest of the presentation on that, which gives you some idea of how these systems work and possibly some of the problems that we have with our animal models as has been alluded to before. We normally are using 80-kg calves. We are focusing just on the central blood pump and energy converter. We are using external electronics and a vent for compliance. Basically, what we are trying to show that we can support one of these animals and that the system is compatible with the physiology. And of course, most important, we are using it to test our system. We have done four experiments to date and our progression has gone from a planned 1-day acute model to a couple of intermediates, and our last one was 45 days.

On these early animals we are using all the blood pressure instrumentation we need: inlet and outlet pressures on both sides. These animals therefore are fairly risky in that there are indwelling catheters in them. One of the things we have learned over the years is that a calf is not a human, and it is very difficult to take a human configured system and try to force it into a calf. Therefore we have changed the inlets a little bit to help us get better anatomical fit in the calves. The big difference is that the outlet on the left side is bent so it intercepts the aorta.

I would like to give some data now from a 45-day experiment. When we plot out all the data points we took, they average around 10 mm Hg in the right atrium. On the left side it is a little more scattered, but it would average out about 16 mm Hg. One of the things about these animals, and in particular one, he maxed our pump out the first night. He was running at 10 L/min essentially on day 1 and that is where he stayed. Although this is a good healthy workout for our actuator, it does not do much for our control system, which indicates a problem we have in the model. We maxed out at 160 beats for the whole experiment and our power draw was 15 W throughout. In some of the earlier experiments where the calves were not as healthy, we were able to go to the lower flow rates and verify that indeed our control system does function like we intend it. But we need to have a lot more experience with that.

To summarize the in vivo results, we can maintain the hemodynamics of these animals. The fit is extremely good. We have not had any hemolysis or thrombus problems. The diaphragms come out absolutely clean after the experiment. What we are going to be doing is continuing the in vivo studies, our sequence of involving the other system integration elements. This is due to come in a couple of months. We will add that into the energy converter, add the compliance TETs in with the rest of the systems, and by the end of this program we will be doing a total.

I think I speak for all of us when I say that these programs are supported by the devices and technology of the National Institutes of Health, and as I understand the plans we have another couple years to go on the current contracts. There probably will be a follow on for 3 or 4 years, which puts us in a time frame such that we probably would be ready to use human implants on a trial

basis somewhere in the year 2000. That is the time line we're working on.

MODERATOR HAHN: Thank you so much, Mr Butler, for this extremely nice presentation. Now we will ask Dr Kung to come here and give his report.

DR KUNG: This is a collaborative effort between Abiomed and the Texas Heart Institute on the development of the electrohydraulic total artificial heart. Because I am last on the agenda I thought the best thing for me to do is to focus on the specific and unique features of our system instead of going into the description of the entire system.

External parts of the system are battery electronics including a TET, internal battery, blood pump, energy converter, hybrid electronics, and sensors for the control of the system. I will describe how our energy converter works, how our blood pump interfaces with the atria, the design of the inflows for the pump, and how the compliance or rather the management of the left and right flow differences is done. I also will give some information on our *in vivo* results.

The system is electrohydraulic, and the difference between our electrohydraulic system and that of Nimbus, which I can describe as also electrohydraulic but electrohydraulic converted to mechanical energy, is that we use a direct electrohydraulic drive of the flexing membrane, which is what the Utah group does also. The difference between our system and the Utah system is that we use a unidirectional rotary pump. In other words, the rotary pump is not reversed on every cycle. Fluid reversal is accomplished through an electromagnetic fluid valve. The blood contacting part of the system is designed to be smooth and seamless, and it uses angioflex, which is a polyurethane proprietary to us, and also trileaflet valves made of the same material. We use blood as the volume compensation: I believe we are the only ones taking that approach.

As you heard yesterday, if you have a biventricular support system—in this case this is also classified as biventricular—you have to make sure that the left flow and the right flow somehow match or the difference matches the bronchial shunt. In current systems that have been used clinically you have to manage this by essentially dialing in the flow so that you do not flood the lungs. When you flood the lungs that means the right side is flowing too much. One of the manifestations of that is that the left atrial pressure goes up. If the left atrial pressure goes up you can think of a way of using that as a means of feeding back to your system.

Because for a total artificial heart you obviously cannot keep on dialing the right side flow, you have to use what physiological information is provided by the artificial heart and the living system to control or feed back to adjust the right side flow. There is a hydraulic pump with a fluid switch that switches the fluid back and forth. To manage the left and right side flow, we have put a shunt flow in the hydraulic circuit and placed that in reference to

the left atrial pressure, which means that you can put a flexible diaphragm in contact with the left atrial reservoir. If the left atrial pressure goes up the shunt flow increases in the hydraulic circuit. When the shunt is larger to the right side of the hydraulic chamber, it reduces the amount of blood that is being drawn into the right-sided blood pump. So as the left atrial pressure goes up there is less stroke volume on the right side, and as the left atrial pressure goes down there will be more right-sided stroke volume. One of the advantages of this is that the flow compensation characteristics would not vary over time. In long-term studies we are trying to demonstrate some of these characteristics.

I would like to talk a little bit about the control algorithm. With it we have taken a very simple approach to control the system. In the hydraulic circuit there are pressure transducers, one pressure transducer that measures the filling pressure during the fill cycle of either the left side or the right side. That information is used to control the hydraulic pump. If you have a high end-diastolic pressure on one beat it senses that pressure and then it tells the pump to go to pump a little bit harder on the next beat, so you are trying to bring the end-diastolic pressure to a level that you have preset, whether it is zero or some number that is close to zero filling pressure. The control algorithm is also responsive to afterload because the afterload changes affect the pumping rate or the filling rate. Once you change the filling rate you change the end-diastolic pressure, which then is sensed again, changing the pumping speed of the rotary pump. The other control is focused on trying to make every stroke a full stroke. We have an optimal sensor in the system that monitors the diaphragm position. That information is then used to determine the beat rate of the system. If there is a lot of fluid or if the atrial pressures are high, the beat rate will increase to maintain the full stroke and at the same time to try to bring the end-diastolic pressure down.

Now let me go to the energy converter. There are two channels that connect the hydraulic chambers to the energy converter chamber, so the flow of hydraulic fluid can go either way on each beat. It reverses the flow. As I say, there is a unidirectional rotary pump and a centrifugal one pumping hydraulic fluid. There is a switching valve concentric to the pump that assumes two different positions, which then opens a set of ports, which then directs the flow either from one pump to another or vice versa. It is actually a very simple system. You are switching the hydraulic chambers, which pumps the blood to the two alternate pumps. This is an alternating pumping system.

Now let me describe briefly the blood pump. The valve that is used is a polyurethane trileaflet valve. Concerning the experience that we have on these blood-contacting components, the valves have gone about 400 million cycles *in vitro*. The pumps we have tested up to 100 million cycles, and *in vivo* about 150 days.

The design of the whole system is to achieve a seamless blood contacting surface. Now in the inflow region, where you have tissue and cuff in contact and sutures that hold the cuff and the tissue together, because we have

discontinuities, it is much better to have a cuff that can promote growth of tissue. But to avoid ingrowth into the inflow of the device, we have made a rough surface on the cuff and a smooth surface in the device. The cuff will be sewn onto the atrial remnants and then the rest of the device will be snapped into the atrial cuff, so this is a quick connecting approach. By this approach there are no end-to-end seams. To get around this rough and smooth configuration, we actually have a smooth surface tube project into the atrial cuff. This provides a tissue barrier to stop the growth of tissue. It is helped by the fact that you have flow going in this way and you probably have some recirculation, which prevents tissue from climbing up the smooth step. The protrusion into the atrial cuff is about 3 mm in height, and in *in vivo* studies it does act as a barrier quite well. It essentially tries to keep away blockage problems.

The system actually can operate at more than 8 L/min, but at 8 L/min it takes about 20 W.

In our chronic studies, we will concentrate on system integration; we will include hybrids, TETs, and *in vitro* study as well as the liability evaluation in this program.

MODERATOR HAHN: Thank you for this very interesting lecture. There are plenty of problems we could discuss, but first I should like the audience to ask questions, because the time is extremely limited.

DR D. GLENN PENNINGTON (St. Louis, MO): I would like to ask Dr Pierce about those animals that he showed us. What is the stage of development of those animals? Is that an integrated system? In other words, are those implanted electronics? And is that an implanted compliance chamber? How complete is the system we are seeing in those animals?

DR PIERCE: Well there is really a progression. As I mentioned, the animal that is now over 11 months does not have energy transferred by the coil system. We do have another animal that we have subsequently operated on that has implanted batteries, a closed system, and energy transfer by the primary and secondary coil. The only thing that we are lacking now is the ability to talk to our system and get information in and out of it. Other than that, the system is pretty much complete.

MODERATOR HAHN: Another question? Doctor Champsaur?

DR GERARD CHAMPSAUR (Lyon, France): What is the projected price of the total artificial heart using your current techniques?

DR KUNG: All of us probably will have an answer to that. Let me just start by saying that we have in the design of the system and its development always tried to make it

simple enough so that things are not that expensive. Our estimate is that we can do it, once the whole technology is developed, for about \$25,000. Now I am sure that some of the people here would think otherwise, but we have done some evaluation of that.

MR BUTLER: In our particular case, we project a cost between \$35,000 and \$50,000. Actually, our total heart device is cheaper than our left ventricular assist system because it is simpler.

MODERATOR HAHN: Doctor Olsen, do you have a comment?

DR OLSEN: I think when we consider the additional constraints and costs of Food and Drug Administration approval, it will be the upper limit of Mr Butler's estimate of \$50,000.

DR PIERCE: I think it is important to note that there is nothing inherently expensive about these devices. The roller screws we use in our units cost, I think, \$1,000. The motors are \$400 or \$500, and there is one fairly complex titanium machined part, the costs of which would not be high if you were going to make a bunch of them. But by the time you put in the animal experiments and all of the careful controls that have to be done before something like this can be sold, the price escalates. I would estimate \$50,000, something like that, and I do not think these total hearts are going to be more expensive than the left ventricular assist devices. There is very little additional complexity to them.

MODERATOR HAHN: Another question?

DR PAUL DIDISHEIM (Bethesda, MD): I would like to ask each of the panelists about thromboembolism. Because we know from past experience that an implanted device can look free of thrombus or relatively free of thrombus and still be a generator of thromboemboli, I would like to ask each of the panelists if they have yet had an opportunity to look at end organs, specifically the kidney, which has in the past been a useful thromboembolus trap.

MODERATOR HAHN: Doctor Kung, would you answer?

DR KUNG: Yes, in our experience, we have not had any long-term experience with the total artificial heart yet. But the technology that we have used in the permanent ventricular assist device is really quite similar to what we have here. And there we have had experience up to 5 months with no infarcts or emboli.

MODERATOR HAHN: Another comment from the panelists?

MR BUTLER: We just completed a 45-day experiment with the total heart. That is our longest. But it does have the biolyzed coating that we have had considerable experience with on the left ventricular assist devices. This 45-day animal was run without anticoagulants, and I do not think all the histology data are in yet, but the gross examination showed no infarct problems.

DR OLSEN: Our limited experience in acute experiments with the electrohydraulic system would not lend itself to respond there. We have seen none, however, in 9 days.

MODERATOR HAHN: Doctor Pierce?

DR PIERCE: If we follow the design principles that we have all learned the hard way over the past 20 or so years and then we keep our animals on warfarin sodium and their renal function has been basically normal, the devices have been clean when they have been taken out. So thromboembolism has not been a problem in our case. We have had broken wires. We have had moisture get into the devices. We have had just about everything you can think of. But thromboemboli have not been a problem.

MODERATOR HAHN: I guess I must stop this session. It is a great pity, because we had so many questions to ask about these electromechanical devices that will be the future in cardiac replacement.

Circulatory Support in Infants and Children

D. Glenn Pennington, MD, and Marc T. Swartz, BA

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Although the last decade has brought dramatic improvement in patient selection and postoperative management of adults and children undergoing advanced mechanical circulatory support, technological advances have been largely limited to the adult population. Intraaortic balloon pumps are technically feasible, but their efficacy has been questioned and their use has been limited in children. Over the last decade, extracorporeal membrane oxygenation has become the most commonly used method of mechanical circulatory support in children who have severe cardiac failure after cardiac operations. Additionally, a small number of infants and children have been supported with extracorporeal membrane ox-

ygenation as a bridge to cardiac transplantation or as temporary support during reversible myocardial failure due to lesions such as viral myocarditis. More recently, a small number of pediatric patients have been supported with centrifugal and pneumatic devices, particularly after cardiac operations. Surprisingly, many of these patients did well with left ventricular support only. The overall children's survival rates in the myocardial recovery group are better than those in adults. However, current pediatric devices do not provide support for greater than a few weeks, making bridging to transplantation less feasible than in adults.

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Circulatory support of patients with failing hearts has been a goal since the 1950s, when Stuckey and associates [1] used a heart-lung machine to support patients with cardiogenic shock after myocardial infarctions. Subsequently, Dennis and co-workers [2] used a left heart bypass system in 2 patients. One of the early attempts at supporting a child occurred in early 1963, when Spencer and colleagues [3] supported a 6-year-old girl in whom severe cardiac failure developed due to pulmonary hypertension after repair of a ventricular septal defect. Apparently she was successfully supported with venoarterial bypass for a period of hours, but died of arrhythmias 24 hours later. In 1967, DeBakey [4] supported a 16-year-old girl with a left atrial-axillary ventricular assist device for severe cardiac failure after mitral valve replacement. The device performed well and she was a long-term survivor. Subsequently, circulatory support of adult patients has been accomplished with an array of devices for cardiac failure after cardiac operations, for acute myocardial infarction shock, and as a bridge to cardiac transplantation [5]. In spite of the development of more sophisticated devices for adults, the need for miniaturization of these devices has delayed their use in children. This report reviews the current systems available for children and summarizes the clinical results.

Some of the data contained in this article were obtained from the Registry for Mechanical Assist Devices and Total Artificial Hearts sponsored by the American Society for Artificial Internal Organs (ASAIO) and the International Society of Heart and Lung Transplantation (ISHLT) and reports from the Extracorporeal Life Support Organiza-

tion. Figure 1 shows the number of cases of advanced mechanical circulatory support in children per year, from 1981 to 1990.

Intraaortic Balloon Pumps

Since the pioneering work of Moulopoulos and associates, who introduced the use of counterpulsation by means of an intraaortic balloon in 1962 [6], the intraaortic balloon pump has been the primary method of mechanical support of adults with cardiac failure [7]. Although the use of intraaortic balloon pumps in children has been limited, it has been effective in some cases [8-10]. In a 10-year experience at the Toronto Hospital for Sick Children, 38 patients received intraaortic balloon pumps, with 14 survivors, for a 37% overall survival rate [10]. Recently, Christensen and associates [11] of Primary Children's Hospital of Salt Lake City, UT, reported the use of intraaortic balloon pumps in 29 children, 12 (41%) of whom survived. Their survival rates were highest in children older than 5 years. Of 10 infants treated with intraaortic balloons, 2 survived. Near systolic or suprasystolic diastolic augmentation was achieved less often in children younger than 2 years. Del Nido and colleagues [10] reported the successful use of an intraaortic balloon pump in a 2-kg infant. However, from the Utah experience [11], one would conclude that the outcomes are less favorable in younger patients. In the Toronto series, all 4 children younger than 5 years died, but their experiences occurred before the miniaturization of the balloons [9]. The effectiveness of intraaortic balloon pumps is still limited in small children and infants by increased aortic elasticity, rapid heart rates with small stroke volumes, and difficulty of insertion. Furthermore, the intraaortic balloon pump is often ineffective in patients with predominant right heart failure, which often occurs in children with congenital heart disease. Therefore, it is our opinion

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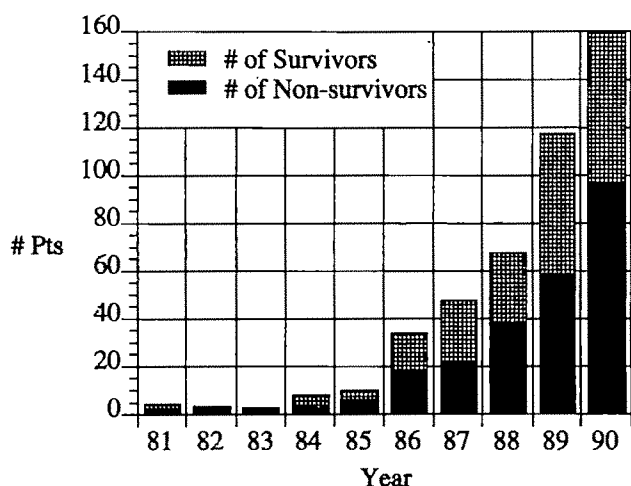


Fig 1. Number of patients and survival in children supported with mechanical circulatory support from 1981 to 1990.

that if intraaortic balloon pumps are to be employed in infants and children, a more complete form of circulatory support should be available to augment or supplant the intraaortic balloon pump if it does not provide optimal support.

Extracorporeal Membrane Oxygenation (Venoarterial Bypass)

The use of venoarterial bypass with an oxygenator for prolonged circulatory support has generally been referred to as "extracorporeal membrane oxygenation" or ECMO. Use of this technique was reported in patients with severe cardiac failure in 1957 and 1965, but it was not commonly used during the 1970s. Indeed, in the National Heart, Lung and Blood Institute-sponsored study of the use of ECMO for severe respiratory failure, patients with concomitant cardiac failure were excluded [12]. Simultaneously, a large, successful experience with the use of ECMO for infants with severe respiratory failure was developed by Bartlett and colleagues [13]. In their experience, the early results of ECMO for postoperative cardiac failure were disappointing [13]. However, subsequent experience demonstrated the effectiveness of ECMO in some postcardiotomy patients. In 1982, we initiated an ECMO program at Cardinal Glennon Children's Hospital of St. Louis University to support children after cardiac operations. Of 65 postcardiotomy patients treated with ECMO for cardiac failure over the ensuing 9 years, 44 (68%) were weaned from the ECMO circuit and 23 (35%) were long-term survivors [14]. During the last 3 years in which 26 postcardiotomy patients were treated with ECMO, 20 (77%) were weaned and 13 (50%) survived [14]. In our series of 65 patients, the most common complications were bleeding requiring reexploration (44 patients), sepsis or mediastinitis (20 patients), neurological complications (18 patients), and renal failure (25 patients). In spite of this high complication rate, survivors have generally done well after hospital discharge. We

have been unable to determine which pre-ECMO factors would ultimately determine survival after placement on ECMO. Although it is clear that some cardiac defects are so severe that survival is impossible, this is not often known at the time the decision to use ECMO must be made.

A review of the literature (Table 1) reveals a rather wide range of survival rates from 30% to 70% in infants and children undergoing ECMO support for postcardiotomy heart failure over the last 10 years [14-18]. Although early survival rates were less than 50%, rates during the last 3 to 5 years exceed 50% in some centers [14, 16-18]. However, in a larger collective series of 453 pediatric patients supported with ECMO for cardiac failure, the "survival rate" was 43%. These data were accumulated in the Extracorporeal Life Support Organization Registry, an international registry for extracorporeal life support in pediatric patients. Although these data are useful, they are somewhat misleading, because their "survival rate" of 43% represents all patients who were weaned from the ECMO system. The survival to hospital discharge is not known, but judging from reports from other centers, it is almost certainly lower than the wean rate. In spite of the improved recent results of ECMO, it is unlikely that survival rates of patients having ECMO for cardiac failure will ever equal those of patients undergoing ECMO for respiratory support. Current limitations to survival include the complexity of the heart defects necessitating ECMO, the need for continued heparinization to prevent clotting in the ECMO circuit, and the higher incidence of infection related to the surgical implantation of the system.

Table 1. Extracorporeal Membrane Oxygenation for Postoperative Cardiac Failure

Center	No. of Patients	Weaned	Survived	% Survival
St. Louis University (Cardinal Glennon Hospital) (1982-1991)	65	44	23	35%
St. Louis University (Cardinal Glennon Hospital) (1988-1991)	26 ^a	20 ^a	13 ^a	50%
University of Michigan (1971-1989)	10	3 ^b	3	30%
Wayne State University Children's Hospital of Michigan (1984-1989)	36	22	21	58%
University of Pittsburgh (1981-1987)	10	8	7	70%
University of Arkansas (18 months)	24	18	13	54%
Washington University Children's Hospital (1985-1988)	12	8	5	42%
Total	157	103	72	46%

^a Excluded from total.

^b Incomplete data.

Several controversies continue over how to best apply ECMO support. The sites of cannulation differ among ECMO centers. Some centers use right atrial-aortic cannulation placed through the reopened sternotomy wound, whereas others have used the neck vessels [18]. The advantage of neck cannulation is the omission of the need to reopen the sternotomy wound, perhaps lessening the risk of bleeding from the surgical wound and the risk of mediastinitis. On the other hand, we have been concerned that carotid artery ligation would increase the risk of neurological injury, which is already high in these desperately ill patients. At least some of the patients undergoing neck cannulation have had the neck vessels repaired at the time of ECMO removal [18]. Femoral and iliac cannulations have also been used, but are not commonly used today. It seems clear from our clinical experience at Cardinal Glennon Children's Hospital that left heart cannulation may be required in some patients, because arteriovenous ECMO does not provide adequate decompression of the left ventricle [19-21] in patients with failing hearts, and actually increases left ventricular afterload [19, 20]. Left ventricular decompression can be accomplished with a relatively small left ventricular cannula [21]. Although left atrial cannulation may not provide complete left ventricular decompression, we have found it to be effective in most patients requiring postoperative ECMO. Whether left atrial or left ventricular cannulation is employed, it seems clear that some ECMO patients will require left heart support.

Ventricular Assist Devices

Ventricular assist devices (VADs) have been available in a limited way for children since the late 1970s. We employed a centrifugal VAD (Medtronic Corporation) in 4 children at Cardinal Glennon Children's Hospital during that period, with no survivors [22]. The causes of death in these 4 patients were primarily progressive right ventricular failure. These experiences prompted us to employ the ECMO system in children because it would provide better biventricular support. However, recent experience with VADs in postcardiotomy children have been more encouraging. Karl and associates [23] reported a 50% survival rate in infants and children with postcardiotomy heart failure supported with a left atrial-aortic centrifugal pump (Biomedicus-Medtronic, Minneapolis, MN). Nine of their patients required the assist device to be weaned from cardiopulmonary bypass in the operating room. Apparently, in their experience, the incidence of severe right ventricular failure with left VAD support was minimal. Furthermore, Hanley and colleagues, at Children's Hospital in Boston, have also employed the Biomedicus-Medtronic centrifugal pump in 9 children with severe heart failure after cardiac operations. In almost all patients they employed left atrial-aortic bypass, and 5 of their 9 patients survived. Several aspects of these studies are interesting and contrary to the more established experience with VAD support of postoperative heart failure in adults. Virtually all the children in these two series were supported with left heart support only, and right ventric-

Table 2. Complications of Postcardiotomy Ventricular Assist Devices (n = 32)^a

Complication	% Survivors (n = 9)	% Nonsurvivors (n = 23)	p Value ^b
Biventricular failure	0	43	<0.05
Bleeding	44	39	NS
Renal failure	22	30	NS
Infection	22	13	NS
Respiratory failure	0	17	NS
Mechanical failure	0	4	NS

^a American Society for Artificial Internal Organs-International Society of Heart and Lung Transplantation Registry. ^b χ^2 analysis.

NS = not significant.

ular failure was apparently not a common problem. This may have been because left VAD flows were kept at a lower rate to not overload the right ventricle. The other surprising finding is that 4 patients in Karl and associates' experience required dialysis during VAD support, and 2 of them were long-term survivors. In our experience with adult VAD support, there were no survivors among patients requiring dialysis during VAD support [24]. Table 2 lists the complications encountered in postcardiotomy VAD survivors and nonsurvivors (age < 18 years). Biventricular failure was the only complication that significantly affected survival.

The other area in which VADs have been useful in the pediatric population is in association with cardiac transplantation. Although bridging to transplantation has been quite successful in adults [25], it has been more difficult in children. Successful bridging has been accomplished in some instances. For example, at the University of Pittsburgh, 7 children have been successfully bridged to cardiac transplantation using an ECMO system, and 5 of them have actually survived transplantation (Del Nido PJ; personal communication, Oct 1991). Likewise, the use of circulatory support has been employed in the postoperative period after cardiac transplantation with some survivors [26]. In our own experience at St. Louis University, we employed ECMO in 6 patients after cardiac transplantation, with 2 survivors. Our first survivor lived 7 years but died after his second transplantation. A 1-year-old girl with severe biventricular failure is well 2 years after transplantation.

The primary limitation to the use of these devices for bridging to transplantation has been the miniaturization of the more sophisticated systems. However, at least two centers report the use of more sophisticated devices in children. The Berlin heart has been used successfully in children (Hetzer R; personal communication, Nov 1991), and the Japanese experience includes several children who were successfully supported with assist devices [27]. Bridge to transplantation data from the ASAIO-ISHLT Registry are shown in Tables 3 and 4. There were no significant differences in the percentages of survivors versus nonsurvivors in any of the postoperative complications. The survival rate after transplantation of 71% is comparable with that of adults [25].

Table 3. Complications of Bridging to Transplantation With Ventricular Assist Device and Total Artificial Heart^a

Complication	% Survivors (n = 10)	% Nonsurvivors (n = 9)	p Value ^b
Bleeding	50	22	NS
Renal failure	40	22	NS
Infection	20	0	NS
Biventricular failure	10	11	NS
Respiratory failure	10	22	NS

^a American Society for Artificial Internal Organs–International Society for Heart and Lung Transplantation Registry. ^b χ^2 analysis.

NS = not significant.

It is apparent that miniaturization of the more sophisticated assist devices in the United States is imperative in order that the pediatric population be served, as well as adults. Devices to support infants with hypoplastic left heart syndrome might make more cases of transplantation possible. The advantages of several weeks of VAD support in heart failure patients are the ability to reverse organ dysfunction, eliminate edema, improve nutrition, and promote muscle gain. All of these features lead to a better result after transplantation. However, to provide these benefits, the devices must allow for ambulation and active exercise, which cannot currently be accomplished with ECMO and centrifugal VADs. It is now anticipated that the present decade will see the implantation of a permanent, totally implantable electrical left ventricular assist system in patients with chronic severe cardiac failure. Perhaps a totally implantable biventricular replacement device (total artificial heart) will follow within a few years. However, these devices are being designed for adults, so that the time when such devices might be made available to children and infants is not known. Some very preliminary work is being done [28], but currently seems far away from clinical trials. It is clear that cardiac trans-

plantation cannot provide enough donor hearts to satisfy the need for cardiac support in the younger population. Therefore, work must progress toward the development of more sophisticated temporary and permanent devices for infants and children.

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Circulatory Support With Shock Due to Acute Myocardial Infarction

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Cardiogenic shock after acute myocardial infarction develops according to the amount of lost myocardium, function of remote myocardium, and the phenomenon of infarct expansion. Patients treated with mechanical support alone, without additional measures, have a mortality rate of 80%, the same as patients treated medically. Emergency angioplasty and emergency coronary artery bypass grafting can reduce mortality in certain subsets of patients to 40%. Patients with more severe shock and secondary organ dysfunction may be treated with me-

chanical bridging to transplantation with survival rates varying between 45% and 76%. Percutaneous support systems may be used to resuscitate a patient or to temporize, allowing time to perform diagnostic studies to determine if the patient is suitable for revascularization or heart transplantation. Intravenous enoximone may improve cardiac function as well and thus allow better decision making for further therapy.

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Patients in whom cardiogenic shock develops after acute myocardial infarction have a very high in-hospital death rate. This dismal prognosis can be only slightly improved by intensive treatment in coronary care units using hemodynamic monitoring, fluid substitution, and inotropic agents. Mechanical circulatory support with the intraaortic balloon pump improves the hemodynamic condition but not the ultimate outcome [1]. Most patients in cardiogenic shock after acute myocardial infarction have lost 40% or more of their myocardium, either acutely or in combination with earlier infarcts [2]. Despite this fact the death rate is not strictly correlated to the mass of necrotic myocardium [3], but also depends on the functional state of remote myocardium [4]. As the amount of myocardium temporarily nonfunctioning is not known in the acute clinical setting, it is difficult to decide which patient will benefit from any type of revascularization. Another option for patients who are transplant candidates is to use mechanical blood pump support to bridge the waiting period until a suitable donor organ is available.

Patient Selection

There are several reasons why left ventricular power failure develops in patients with acute myocardial infarction. If the absolute amount of myocardium lost during the acute event or the addition of old and new infarctions adds to more than 40%, development of shock is highly probable [2, 5]. In addition, patients dying of cardiogenic shock showed marginal extension of the recent infarct and focal areas of necrosis throughout both ventricles in retrospective pathological studies [2].

Infarcted regions may undergo expansion by stretching of myofibrils during the first days. This increase in ventricular volume is correlated with hemodynamic deterioration and is the substrate for left ventricular aneurysm formation [6-8]. Reperfusion appears to limit this phenomenon by development of contraction band necroses, myocardial stiffening, and enhanced reparative processes [9, 10]. The development of myocardial infarction is often evolutionary, and infarcts of different age and signs of infarct extension at the margins of vital tissue are observed [2, 7].

The function of remote, noninfarcted myocardium determines the degree of compensation for lost contractile force. In general the stress produced by infarction causes deterioration of the metabolic condition of the entire heart [11, 12]. The amount of hypercontractility is inversely related to infarct size [4, 13-15]. In addition, blood flow to viable tissue supported by a stenotic noninfarct-related vessel may be severely impaired by occlusion of the culprit vessel [16, 17].

As the functional and pathologic changes leading to ventricular power failure are so complex, there must be several therapeutic strategies adapted to the individual circumstances of the patient. Successful percutaneous angioplasty of the infarct-related vessel within 12 hours of the onset of chest pain reduced the in-hospital mortality rate from 60% to 19% in hypotensive patients [18] and from 82% to 33% for patients in cardiogenic shock [19]. Mortality for emergency coronary artery bypass grafting within 18 hours after onset of cardiogenic shock was 7% when protection of the remote myocardium was accomplished with blood cardioplegia [20]. Survival for patients undergoing bypass grafting for shock is reported to be between 66% and 80% [20, 21].

Cardiogenic shock was defined differently in these studies, so the hemodynamic condition of the patients cannot be compared. Mechanical assistance with intraor-

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Table 1. Results of the Use of Mechanical Assist Devices Without the Intention for Later Heart Transplantation

Report	No. of Patients	Weaned	Discharged
Noda et al [22]	2	1	0
Pennington et al [23]	3	2	0
Zumbro et al [24]	1	1	1
Total	6	4	1
ISHT-ASAIO	79	22 (28%)	8 (10%)

ISHT-ASAIO = International Society for Heart Transplantation and the American Society for Artificial Internal Organs.

tic balloon pumps or ventricular assist devices improved heart failure, but in-hospital mortality rate remained at 80% to 90% [1] (Table 1). A decision therefore must be made as to whether the patient should undergo any form of revascularization or should be considered a transplant candidate. To buy time to perform the necessary diagnostic studies, Loisance and associates [25] use a pharmacological bridge concept. In 7 of 10 patients in massive cardiogenic shock after acute myocardial infarction the hemodynamic situation improved after administration of a 1.5 to 2 mg/kg bolus of enoximone. A mechanical device had to be implanted on an emergency basis in only 3 patients [26]. Percutaneous assist devices are also able to stabilize patients for further diagnostic studies. Patients not considered transplant candidates may be offered revascularization techniques as an alternative even at high risk or, in the future, may be candidates for totally implantable assist devices.

Percutaneous Devices

There are several options for circulatory support by a quick, percutaneous approach. This avoids the need for a thoracotomy for installation and can be done in the catheterization laboratory. This method can be used to resuscitate patients, to perform diagnostic studies or angioplasty, or to buy time until more definitive measures can be taken. In addition there is experimental evidence that ventricular unloading can significantly reduce infarct size [27]. Reduction in infarct size was related to the degree of pressure unloading of the left ventricle, which is usually only achieved by direct ventricular cannulation [28, 29]. Adding counterpulsation to a percutaneous extracorporeal membrane oxygenation circuit was similarly effective in reducing myocardial necrosis [30, 31].

Mobile extracorporeal circuits mounted on a cart have been made commercially available. In the case of hemodynamic deterioration or during resuscitation one arterial and two venous cannulas are inserted into the femoral vessels using a Seldinger technique. Circulation can be reestablished by this technique as reported by Phillips [32] and Pennington and associates [33, 34], and survival rates are about 20% after subsequent treatment with angioplasty, bypass grafting, or heart transplantation.

The Nimbus Hemopump (Nimbus Medical Inc, Rancho Cordova, CA) can be inserted through a vascular graft sewn to the iliac or femoral vessels under fluoroscopic

guidance. It consists of a high-speed rotary pump contained in a perfusion cannula inserted across the aortic valve into the left ventricle. The system is powered and flushed through an axial cable. Insertion can be accomplished within 20 minutes and flow rates up to 3 to 3.5 L/min can be achieved. It definitely adds more circulatory support than does the intraaortic balloon pump, and it is possible to maintain circulation during ventricular fibrillation after sufficient fluid loading [35]. Coronary perfusion is improved, as shown in an experimental model [36]. On the other hand, unloading of a failing left ventricle may diminish its output, with blood flow achieved only by the Hemopump. As its flow maximum is limited, reversal of shock or recovery of organ function is often not achieved. Therefore most successful applications are reported when only short-term support was necessary [37, 38]. Deeb and associates [38] reported 3 surviving patients after successful implantation in 5 patients with acute myocardial infarction. In 3 patients the device could not be inserted due to technical reasons (Table 2).

Dennis and colleagues [39] designed a specially curved cannula containing an aspiration needle and a retractable knife to perforate the interatrial septum and thus to install left heart bypass. Lefemine and Dunbar [40] used percutaneous biventricular bypass with left ventricular and right atrial withdrawal, without the use of an oxygenator. For both methods only limited clinical experience is reported.

Bridging to Transplantation After Acute Myocardial Infarction

Since the first report of a successful bridge to cardiac transplantation for acute myocardial infarction shock [41], the combined registry of the International Society for Heart Transplantation and the American Society for Artificial Internal Organs (ISHT-ASAIO) lists a total of 262 patients treated with mechanical blood pumps to stabilize hemodynamics for cardiogenic shock complicating acute myocardial infarction. The devices used were total artificial hearts and pulsatile and centrifugal ventricular assist devices for either left, right, or biventricular support. Sixty-three of the 262 (24%) survived to hospital discharge. However, the treatment modalities of these patients were quite different. Seventy-nine patients were treated without the intention for later heart transplantation. Twenty-eight percent could be weaned from the

Table 2. Results of Percutaneous Mechanical Support

Report	Device	No. of Patients	Weaned	Discharged
Kanter et al [34]	PCPB	15	11	2 (13%)
Phillips [32]	PCPB	14	9	4 (29%)
Deeb et al [38]	Hemopump	5 (8)*	3	3 (60% [38%])*

* In 3 patients the device could not be inserted.

PCPB = percutaneous cardiopulmonary bypass system.

device, and only 10% were discharged from the hospital. Of the 76 patients who had an artificial blood pump implanted for later heart transplantation, 46 (60.5%) underwent transplantation and 34 (44.7%) could be discharged. Seventy-four percent of transplanted patients were discharged, indicating that mortality after the bridge period is somewhat higher than after conventional heart transplantation in mortally ill patients [42]. For the whole series there was no difference in the survival after support with centrifugal or pneumatic blood pumps. The survival for patients who had a total artificial heart implanted was 15 of 42 (36%). Though not clearly indicated, probably all of them were implanted with the intention of later heart transplantation. Farrar and associates [43] reported 17 patients receiving the Thoratec ventricular assist device system for acute myocardial infarction shock. Thirteen of these underwent transplantation and all of them survived to hospital discharge (76%). This is better than the reported 63% survival rate for the whole series including cardiomyopathies, transplant rejections, and myocarditis and the data for the combined registry (Table 3). This is consistent with the experience that survival rates after the use of ventricular assist devices tend to be better than those after use of total artificial hearts in bridged patients [43, 45-47]. Total artificial hearts have been used mostly before ventricular assist systems became easily available for clinical use, so the better results achieved with assist systems can be explained by the gain in experience. Kormos and associates [45] preferred the use of a total artificial heart over the use of an apicoaortic implantable left ventricular assist device (Novacor, Baxter Healthcare, Oakland, CA) due to the risk of ventricular arrhythmias and dislodgement of the apical cannula. This lethal complication was observed by Lewis and colleagues [26] after implantation of the TCI implantable left ventricular assist device (Thermo Cardiosystems Inc, Woburn, MA) in a patient with acute infarction.

Difficulties arise when one reviews the literature for mechanical circulatory support after acute myocardial infarction as some of the patients are operated on for infarct complications. So it is not clear whether these patients should be considered to receive implants for postcardiotomy shock or acute myocardial infarction shock. Survival for postoperative mechanical assistance is 24% (107 of 451 implants) [48] as reported by the ISHT-

Table 3. Rate of Transplantation and Hospital Survival After Use of Mechanical Blood Pumps as a Bridge to Transplantation After Acute Myocardial Infarction Shock

Report	No. of Patients	Transplanted	Discharged
Farrar et al [43]	17	13 (76%)	13 (76%)
Loisance et al [44]	3	2	2
Zumbro et al [24]	4	1	1
Our results	6	3	2
ISHT-ASAIO	76	46 (60.5%)	34 (45%)

ISHT-ASAIO = International Society for Heart Transplantation and the American Society for Artificial Internal Organs.

Table 4. Survival Rates for the Use of Ventricular Assist Devices After Operation for Complications of Acute Myocardial Infarction

Report	No. of Patients	Weaned	Discharged
Noda et al [22]	8	6 (75%)	3 (38%)
ISHT-ASAIO	99	45 (46%)	20 (20%)

ISHT-ASAIO = International Society for Heart Transplantation and the American Society for Artificial Internal Organs.

ASAIO combined registry, although survival rates up to 40% may be achieved in experienced centers [49, 50]. Certainly timely implantation of the support device avoiding multiple attempts to wean the patient off extracorporeal circulation is a predictor for outcome [51], and the intention to implant a support device should be part of the surgical strategy in patients with preoperative shock. Noda and colleagues [22] reported a 38% survival rate for patients operated on for shock complicating acute myocardial infarction, whereas Pennington and associates [52] reported a dismal prognosis for patients with perioperative infarction requiring mechanical assistance. Still, in their series perioperative infarction did not preclude myocardial recovery and subsequent weaning from the assist device. The survival rate for patients with mechanical support after operation for acute myocardial infarction shock is reported to be 20% in the combined registry (Table 4).

Our Results

Six patients with cardiogenic shock complicating acute myocardial infarction were transferred to the Second Surgical Department of the University of Vienna for mechanical circulatory assistance as a bridge to heart transplantation.

The Vienna Heart was designed and is manufactured in cooperation between the Second Surgical Department and the Institute for Biomedical Engineering of the University of Vienna and the Ludwig Boltzmann Institute for Cardiosurgical Research in Vienna. A 65-mL ventricle is vacuum-formed from sheets of thermoplastic polyurethane (Pellethane). The two-layer pump membrane is solution-casted; the second layer also lines the inner surface of the pump housing, guaranteeing a seamless transition between housing and membrane. Flow is directed by a 29-mm (inflow) and a 27-mm (outflow) tilting-disk valve (Sorin, Italy). A 51F Sarns lighthouse cannula, bent to 90 degrees and coated with Pellethane, is used as inflow and a 12-mm expanded polytetrafluoroethylene graft is glued to the outflow cannula (Fig 1). Left heart bypass was always instituted between the right upper pulmonary vein and the ascending aorta. The ventricles are powered by a pneumatic drive unit [53]. Membrane position and motion was estimated by analysis of drive-line pressure and gas flow.

All patients were transferred in a state of cardiogenic shock (Table 5). They had been treated in coronary care units for several days after first or recurrent (patients 2, 4,

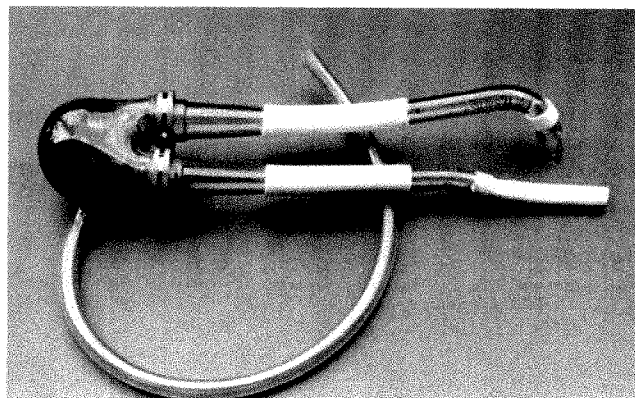


Fig 1. The Vienna Heart left ventricular assist device. The housing is vacuum-formed, and the two-layer membrane is solution-casted. A modified lighthouse cannula is used for inflow and a vascular graft bonded to a cannula is used for outflow.

and 5) acute myocardial infarction. Four had renal failure, 1 of them treated with hemofiltration; 2 had impaired liver function with disorder of the coagulation system. A 65-year-old man had signs of adult respiratory distress syndrome indicated by roentgenogram and blood gas analysis after experiencing a large anterior infarction and cardiogenic shock. He underwent successful transplantation after 5 days of circulatory support (Fig 2). None of the patients had undergone coronary angiography due to their unstable hemodynamic condition. In all patients except patient 1, in whom no adequate pump flow could be achieved, the hemodynamic situation improved and organ function recovered. Recurrent ventricular fibrillation developed in 4 patients while they were supported by left ventricular assist. In 2 patients (patients 5 and 6) prolonged attacks of ventricular fibrillation led to multiorgan failure and neurologic deficit, respectively. Both had recovered initially, and the arrhythmia must be considered the main reason for the fatal outcome. Patient 4 improved hemodynamically and could be extubated 3 days after left ventricular assist device implantation. Urine flow had normalized, although serum creatinine level remained elevated. Severe graft failure developed on the first day after transplantation, with metabolic acidosis lowering pH to 6.9. Despite recovery of cardiac function

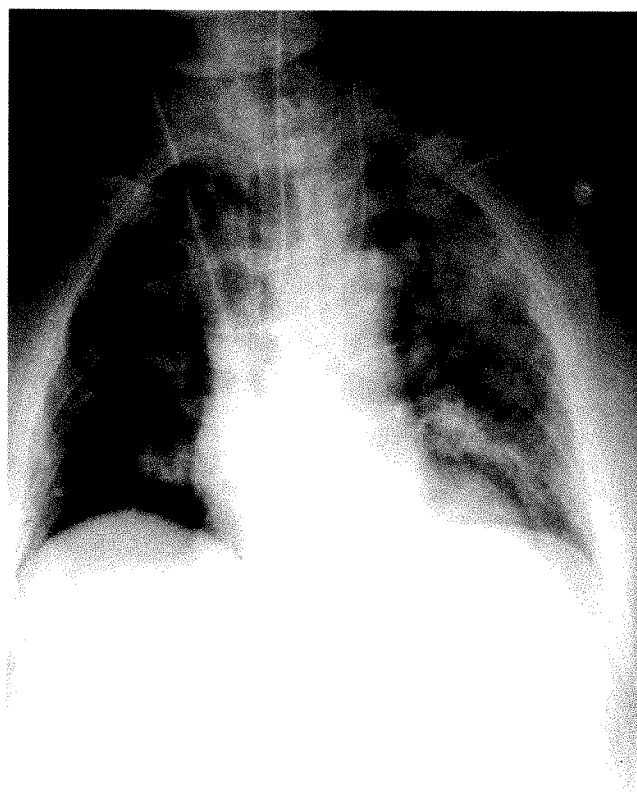


Fig 2. The chest roentgenogram of patient 3 shows signs of adult respiratory distress syndrome the first day after left ventricular assist device implantation, despite normal to low left atrial pressures.

he died of multiorgan failure acquired during this period of hypoperfusion.

Patient 2 had an elevated white blood cell count of $40 \times 10^9/L$ ($40,000/\mu L$) but no proven infection other than severe stomatitis. His renal failure necessitated hemofiltration before left ventricular assist device implantation. On the first postoperative day 17 L of fluid was necessary to stabilize his hemodynamics. In the later course multiple blood cultures were positive for *Klebsiella*, enterococci, and *Candida*. Under antibiotic treatment his organ functions stabilized, and as the implanted left ventricular assist device or the left ventricular thrombus was considered the septic focus, he underwent successful transplan-

Table 5. Characteristics of the 6 Patients Treated With Left Ventricular Assist Device Support With the Intent of Later Heart Transplantation at Our Institution

Patient No.	Age (y)	Creatinine (mg/dL)	Diureses	Bilirubin (mg/dL)	Lungs	Tx	Survival	Complications
1	48	2.4	Oliguria	6.6	...	-	-	Leg ischemia, MOF
2	41	1.7	Anuria (HF)	16	...	+	+	Sepsis
3	65	2.6	Oliguria	0.9	ARDS	+	+	ARDS
4	60	4.3	Anuria	1.3	...	+	-	Graft failure
5	61	2	Oliguria	0.6	PE	-	-	Neurologic deficit, VF
6	41	0.8	Oliguria	0.6	PE	-	-	VF, MOF

ARDS = adult respiratory distress syndrome; HF = hemofiltration; MOF = multiorgan failure; PE = pulmonary edema; Tx = heart transplantation.

tation after 22 days of support. All consecutive blood cultures were negative and he is alive and well 2 years later.

Comment

Decision making in the situation of cardiogenic shock complicating acute myocardial infarction is complex as optimal treatment depends on diagnostic information frequently not available in the acute setting. In addition to the amount of myocardium lost by the acute and earlier infarctions, the function of remote myocardium, infarct expansion, and infarct extension lead to left ventricular power failure. This range of causes explains why a variety of treatment modalities are reported to be successful in treatment of cardiogenic shock. The results of studies using different therapies are difficult to compare as the definition of cardiogenic shock varies and patients are treated at different times from onset of chest pain or cardiac failure.

Mechanical assistance using intraaortic balloon pumps or mechanical blood pumps was able to relieve cardiogenic shock, but in-hospital mortality and 1-year mortality were not improved significantly compared with medical treatment alone, ranging between 71% and 90% [1, 54] (see Table 1).

Restoring adequate blood flow to the myocardium may limit infarct size [55], avoid infarct expansion [10], or improve the function of remote myocardium [4]. Once cardiogenic shock is established it is usually too late to salvage myocardium in the infarct area. Despite this, angioplasty done within 12 hours of onset of pain improved survival in shock patients from 18% to 67% [19]. It is worth noting that mortality rates for patients with unsuccessful angioplasties parallel those of medically treated patients. Successful relief of cardiogenic shock is reported in 94% when surgical revascularization of the infarcted, as well as remote myocardium is done within a mean of 3.4 days after infarction [20]. In this study cardiac index was 2.1 L/m^2 and pulmonary capillary wedge pressure was increased to 27 mm Hg preoperatively. In-hospital mortality for the whole series was 18% and 1-year survival was 70%. Most of the late deaths were due to congestive heart failure. Patients operated on later than 18 hours after onset of shock had the worst short-term and long-term prognosis. In a review of 101 patients who underwent emergency coronary artery bypass presented by Bolooki [21], perioperative mortality was 66%.

Farrar and associates [43] reported a favorable outcome in patients with cardiogenic shock due to severe acute myocardial infarction (cardiac index, 1.6 L/m^2 ; pulmonary capillary wedge pressure, 27 mm Hg) after mechanical bridging to transplantation. Thirteen of 17 patients could undergo transplantation and were discharged from the hospital (76%). This survival rate is higher than that for their total series of 72 patients (63%) and the survival rate reported by the ISHT-ASAIO registry for this indication (45%). Although not generally achieved, these data indicate that even patients in severe shock can be managed with a very good outcome.

At this point there are no clear guidelines as to which devices are optimally used. Myocardial infarctions mostly affect left ventricular output, and so left ventricular assist is frequently sufficient to reestablish sufficient circulation. In all patients in our series we had to treat right ventricular failure with inotropes, but shock could be reversed in all but 1. Four of our patients had episodes of ventricular fibrillation while on the device, and in 2 of them these episodes were clearly related to death. Kormos and colleagues [45] thus suggest use of a total artificial heart preferentially in this setting. Biventricular assist is an adequate alternative as this overcomes problems of circulatory failure due to both arrhythmias and right ventricular failure, especially when the right coronary artery is diseased.

In contrast to patients with chronic cardiomyopathy, patients after acute myocardial infarction are not conditioned to hypoperfusion. Thus secondary end-organ dysfunction develops quickly and accounts for the increased mortality after coronary operation for shock [20]. The 2 survivors in our series had organ dysfunction that was considered in the literature to be a contraindication [56]. Still, reestablishing sufficient perfusion allowed for recovery of organ systems.

Percutaneous support was used to resuscitate patients in two series with a 20% survival after subsequent definitive treatment [32, 33, 38]. In addition, such devices may be used to temporize, allowing performance of diagnostic studies necessary to decide which treatment is optimal for the individual patient. In the state of evolving infarction, infarct size may be limited by these techniques as well [27, 31]. New inotropic drugs may be used as well to stabilize patients until the decision for final treatment can be made [44]. Patients with clear contraindications against heart transplantation, which cannot be expected to resolve during mechanical bridging, have the option to undergo revascularization procedures with increased risk or in the future to have one of the permanently implantable assist devices inserted.

Patients after acute myocardial infarction are seen in cardiogenic shock at variable intervals after onset of pain and with various reasons for ventricular failure. The value of different treatment strategies for these patients is not yet established, but revascularization techniques as well as mechanical assistance as a bridge to heart transplantation certainly significantly improve survival rates.

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The Biopump and Postoperative Circulatory Support

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The Bio-Medicus Corporation, Inc, Minnetonka, MN, approached Allegheny General Hospital in 1978 for laboratory testing of a new pump to replace the standard roller pump [1], which had become associated with some of the damaging effects of cardiopulmonary bypass. Our initial attempts at using the Biopump for long-term assist were carried out by coating the Biopump, tubing, and connectors with a graphite-benzalkoniumchloride-heparin solution [2]. A dog was placed on left heart assist for a planned 6-hour study. Early in the experiment, we noted that the graphite material was peeling from the tubing and the Biopump. After 5 hours, the dog was in a state of disseminated intravascular coagulation and the experiment was terminated.

In a follow-up experiment, we used tridodecylmethyl ammoniumchloride to coat the tubing, connectors, and the Biopump. A dog was then prepared for left heart assist. However, when the Biopump was opened to prime the circuit, we noted that the solvent had weakened the strut supporting the concentric cones of the Biopump. Because the experiment had already been started, we decided to continue, but with an untreated Biopump, tubing, and connectors. The dog was placed on assist for 6 hours and survived the procedure. Importantly, coagulation studies were normal. Subsequent to this observation, 5 mongrel dogs were treated with left ventricle to femoral artery bypass using the Biopump for 24 hours at a flow ranging from 1.8 to 3.2 L/min. All animals survived the 24-hour left ventricular assist and recovered without sequelae.

From these and subsequent animal experiments, we made several interesting observations that contrasted to findings with the standard roller pump: (1) no inflow cannula obstruction and cavitation with resultant air embolization occurred, (2) serum hemoglobin levels in the experimental animals remained low, and (3) no anticoagulation was needed when the Biopump was run at 2,000 to 3,000 rpm for periods of up to 2 weeks.

Early Experimental Background

The rationale for use of the ventricular assist device (VAD) after an open heart operation is founded on the premise that reversible perioperative myocardial injury has oc-

curred. Reversibly injured postischemic heart muscle has been termed "stunned myocardium" by Braunwald and Kloner [3] and others. To study the recovery of stunned myocardium, our laboratory developed a model of normothermic ischemia to produce profound global myocardial dysfunction [4]. In the canine model, 45 minutes of global ischemia produced a severe myocardial injury, which was fatal with standard resuscitative techniques [5]. Our model was developed to determine whether such an injury would be reversible when treated with biventricular support using the Bio-Medicus pump.

Briefly, the heart was exposed through a midsternotomy incision and placed on biventricular support with cannulation of the femoral artery, left atrial appendage, right atrial appendage, and main pulmonary artery. The aorta was then cross-clamped for 45 minutes of normothermic ischemia, after which the cross-clamp was removed, resulting in immediate ventricular fibrillation. A beating, nonworking state was then maintained for the next 24 hours. During the initial hours after cross-clamp release, none of the hearts could sustain stable rhythm or blood pressure. After 12 hours of biventricular assist, an attempt was made to wean the dog from left and right ventricular assist by volume loading the heart. Measures of developed pressure and its first derivative (dp/dt) were obtained. At the end of 24 hours, a final attempt was made to wean the dog from the assist pumps. With complete ventricular decompression for 24 hours, developed pressure and dp/dt steadily improved. At 12 hours of assist, developed pressure had recovered to 66% of control, and after 24 hours of support, 7 of the 10 animals were successfully weaned from biventricular assist. Left ventricular function parameters were essentially normal in these animals, and a subsequent analysis of myocardial water content indicated no significant myocardial edema formation. Recovery of myocardial adenosine triphosphate level also closely paralleled the return of ventricular function. By 24 hours of reperfusion, myocardial adenosine triphosphate stores had fully recovered to control levels.

Finally, an analysis of myocardial ultrastructure was useful in that it provided further evidence that the 45-minute ischemic insult was severe but not irreversible. After 45 minutes of normothermic ischemia, there was moderate ultrastructural damage. After 24 hours of support, none of the tissues in any group showed severe myocardial injury with the disruption and flocculent

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density formation of irreversible cell injury. Thus, a full 24 hours of ventricular assist was required for functional, metabolic, and structural recovery.

In a similar model from our laboratory, Demmy and associates [6] attempted to shorten the time for hemodynamic recovery of injured myocardium by administering adenosine-enriched cardioplegia at the end of 45 minutes of normothermic ischemia. Animals treated with adenosine after ischemia had a faster recovery of left ventricular function than did control animals. One hour after weaning from circulatory support, adenosine-treated animals had higher left ventricular peak pressure (110 ± 21 versus 57 ± 36 mm Hg), greater dP/dt ($3,407 \pm 812$ versus $1,510 \pm 1,376$ mm Hg/s), and lower left ventricular end-diastolic pressure (23.8 ± 4.8 versus 34.0 ± 7.2 mm Hg) than the control group. In addition, the recovery of adenosine triphosphate levels was significantly greater in the adenosine-treated group, which correlated nicely with the hemodynamic results. Thus, adenosine clearly accelerated left ventricular recovery and shortened the time required for biventricular assist after a uniform global ischemic injury. The mechanism postulated for this improvement is that adenosine is extracted from the coronary circulation and used to increase the level of intracellular adenosine nucleotides.

Centrifugal Ventricular Assist Protocol

Description of Device System

The ventricular assist device system used at Allegheny General Hospital consists of a commercially available centrifugal vortex pump (Biopump; Bio-Medicus, Inc, Minnetonka, MN) and standard cannulas and tubing found in routine cardiopulmonary surgery. The system can be used for partial circulatory assist or for total replacement of right and left ventricular function.

For left heart support, cannulation is achieved via the left atrium through either the atrial appendage or right superior pulmonary vein, with return via a cannula in the aorta. For biventricular assist, the right atrium is cannulated in standard fashion as for cardiopulmonary bypass, with return via the main pulmonary artery. The following equipment and supplies should be available: (1) Bio-Medicus pump console, (2) Bio-Medicus disposable pump head, (3) Bio-Medicus flow transducer, (4) Bio-Medicus disposable flow probe, (5) sterile 3/8-inch $\times$ 3/16-inch tubing (approximately 10 feet), (6) tubing clamps (four), (7) priming solution (typically 3 L of Plasmalyte A), (8) large sterile basin (5-L capacity), (9) battery pack, and (10) patient management data sheets.

Indication for Use

The Bio-Medicus pump is appropriate for use in several different clinical situations: patients unable to be weaned from cardiopulmonary bypass after a technically successful open heart operation and who are deemed to have potentially salvageable myocardium; patients in cardiogenic shock secondary to idiopathic cardiomyopathy or to acute myocardial infarction and who are candidates for

heart transplantation; patients with postoperative development of cardiogenic shock after a successful operation with potentially salvageable myocardium; and patients in cardiogenic shock after acute myocardial infarction who are not surgical candidates but who might have reversibly injured or stunned myocardium.

Contraindications

Contraindications include active systemic infection, chronic debilitating diseases, neurologic impairment, metastatic cancer, no potentially salvageable myocardium, blood dyscrasia, or any problem obviating heart transplantation.

Cannulation for Left Ventricular Assist

The left atrial cannula (usually 32F or 34F Sarns venous cannula) can be placed through either the left atrial appendage, the right superior pulmonary vein, or the roof of the left atrium.

Typically, the heart is retracted to expose the left atrial appendage or the right superior pulmonary vein. Purse-string sutures with Teflon pledgets are placed in the base of the appendage, or in the right superior pulmonary vein, and passed through rubber tourniquets. The left atrial pressure is raised by restricting the venous return, the atrium is opened, and the cannula is inserted. After the left atrial cannula is secured, it is connected to the inflow line of the Biopump. All air must be excluded from the connection and tubing at this time. The aortic cannula previously placed for cardiopulmonary bypass will be switched to the outflow line from the Biopump at the appropriate time.

Initiation of Left Ventricular Assist

Cardiopulmonary bypass flow is reduced gradually while the left atrial pressure is monitored by either a left atrial line or pulmonary artery wedge pressure. When the left atrial pressure reaches 20 mm Hg, assist flow is initiated. Cardiopulmonary bypass flow is then discontinued, and the venous line is clamped. The aortic arch cannula is clamped and the cardiopulmonary bypass perfusion line quickly removed. The Biopump outlet line is then connected to the arch cannula. All air must be excluded from the connection and tubing at this time. Assist flow is initiated and increased incrementally. The total systemic blood flow (native ventricular output + ventricular assist pump flow) is maintained at $2.2 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$. Left atrial pressure or pulmonary artery wedge pressure is maintained in the 5 to 15 mm Hg range by volume adjustment.

Most patients will have some degree of right heart failure when the left ventricular assist is initiated. If left ventricular assist pumping cannot maintain a $2.2 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ cardiac index with good cannula placement and adequate volume, then right heart failure is present and right heart assist may also be required.

Preparation and priming of the Biopump is completed as previously described. The right atrial cannula placed for cardiopulmonary bypass is connected to the inflow

line of the second Biopump. A pulmonary artery catheter (typically, 22F Bard right-angle aortic arch cannula) is inserted into the pulmonary artery distal to the pulmonic valve and secured with pursestring sutures. Cannulas are brought out through the superior or inferior aspect of the incision. The skin is approximated, whereas the sternum is not. The perfusion lines are securely sutured to the skin and covered with several towels and a large adhesive plastic drape.

When a patient is on biventricular assist, coordination of the left and right flow rates requires manipulation of the pumps sequentially with close monitoring of the pulmonary artery pressure. The right assist pump flow is gradually increased while the left pump flow is incrementally raised to accommodate the right-sided output. The right assist pump must unload the right ventricle efficiently for the left assist to pump a minimum of $2.2 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$. Left atrial pressure should be 5 to 15 mm Hg.

Anticoagulation Regimen and Coagulopathy

After cardiopulmonary bypass, heparin should be reversed with protamine. After returning to the intensive care unit, the patient is not anticoagulated until clotting studies have normalized, after which administration of heparin is started to maintain activated clotting times greater than 150 seconds. The perfusionist on duty is responsible for performing activated clotting time monitoring and determining necessary heparin doses.

Weaning of Ventricular Assist

Weaning is usually not attempted during the first 24 hours of assist support. When the clinical picture is stable and cardiac recovery is suspected, a weaning assessment can be completed in 3 minutes or less. Assessment parameters are documented by the perfusionist on duty as follows. Pump flow is never decreased to less than 1 L/min. At 1 L/min, the activated clotting time must be greater than 180 seconds, and the duration of time at this flow must not exceed 2 minutes. If the pump flow is to be kept at 1 L/min for longer than 2 minutes, the activated clotting time must be extended to 200 seconds. Biventricular assist devices may be weaned concomitantly in the same manner as single VADs or separately in a stepwise manner.

ASSESSMENT PROCEDURE. For the left ventricular assist device, decrease assist pump flow rate to a rate that induces an increase in left atrial or pulmonary artery wedge pressure to 20 to 25 mm Hg. At the same time, record arterial pressure wave form and monitor for signs of left ventricular ejection. For the right ventricular assist device, decrease assist pump flow to a rate that induces an increase in right atrial pressure to 20 to 25 mm Hg. Concomitantly, record the pulmonary artery pressure in waveform and monitor for signs of right ventricular ejection.

If, after 1 minute of reduced flow, no native ventricular ejection is evident, the assist pump flow is returned to

previous levels. *The combined flow of the native ventricle and the assist pump should always deliver a minimum cardiac index of $2.2 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$.*

If ventricular ejection is noted during weaning, calculate cardiac output by both thermodilution and Fick methods. If substantial recovery is noted, order transesophageal echocardiography as a STAT procedure and return the patient to full VAD support. The staff should perform the transesophageal echocardiography at bedside with the assist pump at 1 L/min flow.

Staged weaning is guided by the degree of cardiac recovery as documented by cardiac output and transesophageal echocardiographic results. When the surgeon determines that the native ventricle can support the required cardiac output, remove the assist cannulas in the surgical intensive care unit or operating room under strict aseptic technique.

Clinical Results

From June 1980 to July 1991, 15,500 patients underwent cardiopulmonary bypass support for cardiac operations at Allegheny General Hospital. Refractory cardiac failure requiring extended support with a centrifugal VAD developed in 77 (0.5%) of these patients. Of the 77 patients, 37 received a left VAD, 4 a right VAD, and 36 a bi-VAD. There were 52 men and 25 women whose ages ranged from 34 years to 74 years, with an average of 56.5 years.

The primary surgical procedures consisted of 52 coronary revascularization procedures, 8 valve replacement operations, 9 combined valve-coronary procedures, 3 combined coronary left ventricular aneurysmectomy procedures, 2 left ventricular aneurysm resections alone, and 3 miscellaneous cases. Nine patients had undergone previous cardiac operations. All patients were protected with cold cardioplegic solution, topical Ringer's slush, and systemic hypothermia. Concomitant intraaortic balloon pumping and pharmacologic support were implemented in all cases. The median sternotomy incision was either left open and packed or sealed with an Esmarck patch. Pump flow rate, which is critically dependent on preload, was manipulated to maintain a cardiac index of $2.2 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ or greater. High flows were maintained, not only to unload and rest the ventricle, but to minimize or eliminate the need for heparin. Flows of less than 2 L/min were only allowed intermittently for assessment of ventricular recovery. Activated clotting times were managed between 150 and 200 seconds. The assist device was implanted in 65 patients immediately after the initial operation and in 12 patients who suffered subsequent hemodynamic deterioration 2 to 48 hours after operation.

Overall duration of assist ranged from 6.5 to 184 hours, with a mean of 52 hours. Average length of assist for left VAD, right VAD, and bi-VAD was 45, 49, and 60 hours, respectively.

Of the 77 patients, 34 (44%) died on the device (non-survivors), 16 (21%) were weaned but died before discharge (short-term survivors), and 27 (35%) were dis-

charged (long-term survivors). Length of assist was not significantly different among the three groups. Long-term survivors were equally distributed between left VADs and bi-VADs (34% versus 37%).

Cardiac failure and associated organ failure was the cause of death for all unweanable patients (nonsurvivors). Four short-term survivors died of sepsis, and 1 died of a ruptured infected femoral artery secondary to a prior intraaortic balloon pump insertion; the remaining deaths were due to progressive cardiac failure.

Postoperative bleeding (83%), which required frequent reexploration and multiple transfusions, was the primary complication of VAD support. Sepsis was the second most frequent complication, resulting in three deaths. Renal dysfunction (creatinine level >2.0 mg/dL) occurred in approximately 35% of all patients, but only 7 patients required dialysis while on support (1 long-term survivor, 5 short-term survivors, and 1 nonsurvivor). Permanent neurological deficits were documented in 6 patients (4 long-term survivors and 2 short-term survivors). The cause (embolic or ischemic) could only be determined in 1 early patient and was thought to be embolic because the event occurred shortly after weaning.

Survival was not significantly influenced by age, sex, primary procedure, aortic cross-clamp time, type of assist, length of assist, or the complications of VAD support. Survival increased significantly ($p < 0.05$) when analyzed by operative era. From 1980 through 1984, survival was 25% as compared with 45% for 1985 through April 1991. This improvement is attributed to increased physician and perfusionist expertise with the system, more aggressive institution of assist support, and better patient selection.

Of the 27 long-term survivors, 17 are alive and 10 are dead. The length of hospital stay for long-term survivors ranged from 15 to 199 days after weaning. The follow-up period after hospital discharge ranged from 0.14 to 10.8 years with a mean of 4.0 years. Observation time for the 17 alive patients in follow-up ranges from 0.4 to 10.8 years, with a mean of 5.4 years. Cumulative 5-year survival for all discharged survivors is 59%.

Six long-term survivors died within 1 year after weaning. Before death, all 6 patients were in New York Heart Association (NYHA) class III. Four patients in NYHA class III died late at 3.1, 3.3, 3.4, and 4.5 years. Cardiac failure was responsible for nine deaths, whereas respiratory failure and pneumonia accounted for the remaining death.

Before operation, 13 of the 17 alive patients were in NYHA class IV, 2 were in class III, and 2 were in class II. Three NYHA class IV patients were in cardiogenic shock, 1 from acute MI and 2 from acute failed percutaneous transluminal coronary angioplasties. Of the latter 3 patients, 2 are in NYHA class II and 1 is in NYHA class I in follow-up. At follow-up, 14 patients are in NYHA class I, 2 are in class II, and 1 is in class III. Ten patients have returned to full working and recreational lifestyles. Four NYHA class I patients are disabled due to noncardiac postoperative sequelae.

Interestingly, 1 long-term survivor returned 2 years after VAD support, underwent uneventful reoperative

coronary artery bypass grafting, and is surviving in NYHA class I with no limitations.

A substantial number of patients with postcardiotomy ventricular failure have reversible injuries as demonstrated by our overall salvage rate of 35% (27/77), our long-term (>3 years) survival rate of 67% (18/27), and our 59% cumulative survival at 5 years for discharged long-term survivors. After 10 years of clinical experience with a centrifugal VAD, we have not yet discovered specific variables that predict recovery in a majority of VAD patients. Our experience also supports the long-term efficacy of VAD support for postcardiotomy patients.

Survivors can reasonably expect to have an excellent quality of life. We, therefore, advocate a continued focused effort on the development of more effective VADs for application in patients after open heart operations.

Future Directions

The Allegheny General Hospital ventricular assist program continues to evolve. Most recently, we have used the Medtronic/Carmeda (Minneapolis, MN/Stockholm, Sweden) extracorporeal membrane oxygenator system in 4 postcardiotomy patients. This system essentially consists of a heparin-coated fiber oxygenator, a disposable Biopump, sterile tubing, and various heparin-coated cannulas for the femoral artery or aortic arch, and for the femoral vein or right atrium.

In one of the more promising recent breakthroughs in the field of biocompatible materials, Olle Larm, chief chemist at Carmeda, successfully developed a technique to bond heparin covalently to foreign surfaces [7]. Larm noted that the heparin molecule has an active component that must be freely exposed to the blood if the chemical chain reactions that prevent coagulation are to take place. Heparin must stand up from the surface as a result of a covalent binding process known as end-point attachment.

Heparin is a naturally occurring polysaccharide, the anticoagulant effect of which occurs primarily through its activation of the enzyme antithrombin. Antithrombin then inactivates thrombin, the enzyme needed in the final pathway for clot formation. The covalent bond developed by Carmeda is situated at the terminal aldehyde group of heparin, allowing the antithrombin binding sites to remain free. Importantly, the process is nonleaching while in contact with blood, saline solution, or albumin. The resulting surface is stable and thrombin-resistant.

The Allegheny General group has used the system in treating 4 patients, with no device failures. The system effectively decompresses both the left and right sides of the circulation. Cannulas have been inserted via the femoral artery-femoral vein approach, as well as through the aortic arch and right atrium. Insertion is not technically difficult. If the device is implanted through the chest, the midsternotomy incision is left open. The femoral approach allows for chest closure. Bleeding has not been a problem, and the oxygenator has been both reliable and effective for nearly 60 hours. The assist device has not required additional heparin, the flow rate has been at least 4 L/min, and the average assist time has been 41 hours.

Coagulation profiles including activated clotting time, platelet count, prothrombin times, partial thromboplastin times, fibrinogen levels, and fibrin split product levels have not demonstrated any damage to the blood elements. Importantly, there has been no problem with disseminated intravascular coagulation.

All 4 patients placed on the device after cardiectomy were successfully weaned from the device. Two of the 4 are considered to be long-term survivors. These 2 survivors both underwent coronary artery bypass grafting procedures for cardiogenic shock complicated by an acute myocardial infarction. A third patient was placed on the Carmeda system after mitral valve repair and concomitant coronary artery bypass grafting for severe ischemic mitral regurgitation. Although weaned from the device, the patient ultimately died of cardiac failure. A fourth patient had development of acute right heart failure after heart transplantation. The device was used as a bridge for 48 hours, at which time a second donor heart was procured. The patient ultimately died of right heart failure.

At this point, the clinical indications for using this device are not defined; however, the system appears to have promise in treating patients with postcardiotomy cardiogenic shock. In addition, it may have a role in treating patients suffering from cardiogenic shock after

acute myocardial infarction or cardiac or multisystem trauma.

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Clinical Experience With Ventricular Assist Systems in Japan

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In Japan, five types of ventricular assist system, including the government-approved National Cardiovascular Center type and the Tokyo University type, were applied to 202 patients as of September 30, 1991. Adult-sized ventricular assist systems were used in 194 patients and a pediatric one in 8. The major primary diagnosis was ischemic heart disease (52.5%). Sixty-three patients in cardiogenic shock with acute myocardial infarction were treated using a ventricular assist system, and the results were fairly good. The predominant indication was failure to be weaned from cardiopulmonary bypass (72.8%), and there was no case of bridging to heart transplantation. Left ventricular assist was performed in most pa-

tients (85.1%). The duration of ventricular assist system application ranged from 1 hour to 70 days, and the mean duration was 6.8 ± 9.6 days. Duration of circulatory support had no relation to the results, and the longest support in survivors was 25 days. The weaning rate was 50.0%, and the survival rate was 26.2%. Main causes of death were heart failure, including unrecoverable heart failure, and multiple organ failure. It should be kept in mind that the decision to use a ventricular assist system should be made quickly, before major organs, including the heart itself, are irreversibly damaged.

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The main purposes for temporary use of a ventricular assist system (VAS) are to maintain the normal circulation irrespective of the severity of heart failure and to restore the failing heart by gradually decreasing the bypass flow as the heart recovers [1, 2]. Research on and development of an artificial heart in Japan started in the late 1950s with the initial objective of cardiac replacement [3]. In the late 1970s, several groups continued to develop a VAS under the stimulus of some successful reports of clinical application from the United States [4-8]. After considerable accumulation of experimental experience, the first clinical application of a VAS in a postcardiotomy patient was performed in 1980 by the Tokyo University group, which was followed by a continuous expansion of clinical applications of VAS using several types of pulsatile blood pump [9, 10].

In response to the demand for availability of such a device, two types of VAS, the National Cardiovascular Center (NCVC) type and the Tokyo University type, were put into clinical evaluation for efficacy and safety under the guidance of the Japanese Ministry of Health and Welfare so as to obtain governmental approval for commercial release. Both types of VAS were approved by the Japanese government in January 1990, and became commercially available after successful results were obtained

in clinical trials conducted on more than 60 patients each [11-13]. In this report, clinical experiences with external pulsatile VASs in Japan are described.

Material and Methods

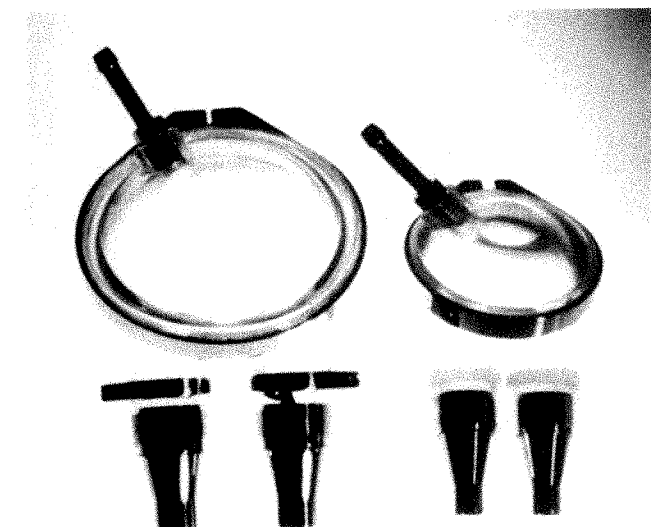
Description of the Ventricular Assist Systems

In the majority of patients, two types, the NCVC type and the Tokyo University type, were used. These two types had already obtained governmental approval as mentioned above. Two other types were used for some clinical cases, the Tohoku University type (pneumatic sac type) and the Thomas Giken type (pneumatic diaphragm type), although these have not yet been approved by the Japanese government. The Thoratec type (pneumatic sac type) also was used in the initial stage of clinical application.

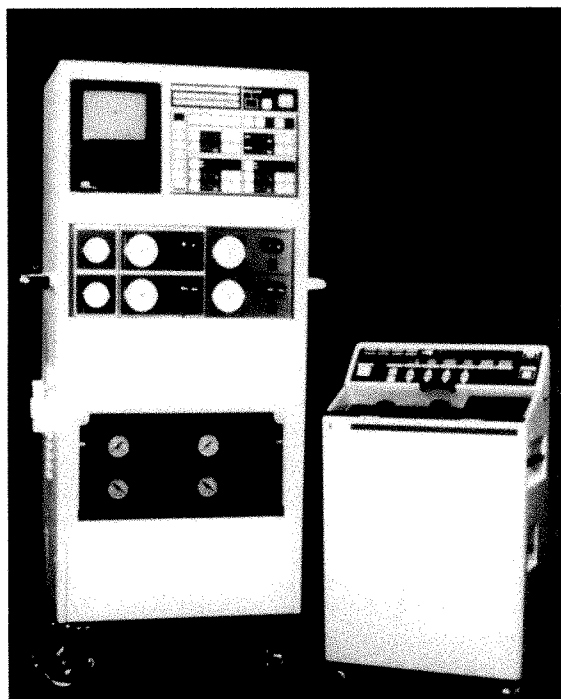
NATIONAL CARDIOVASCULAR CENTER-TYPE VAS. The NCVC-type VAS was developed at the National Cardiovascular Center in Osaka and is manufactured presently by the Toyobo Co, Ltd, also located in Osaka [14, 15]. Two sizes (adult and pediatric) of blood pump are available; the paracorporeal, pneumatic, and diaphragm-type pumps are made of Toyobo TM series segmented polyether polyurethane (Fig 1). The pump body is fabricated without a seam. Two no. 23 Björk-Shiley valves and two no. 21 Björk-Shiley valves are used in the inlet and outlet ports of the adult-sized pumps and pediatric-sized ones, respectively. The effective stroke volumes are 70 and 20 mL, and the maximum outputs are 7.0 and 2.4 L/min, respectively. It has been proved in animal experiments that no antico-

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A



B

Fig 1. The National Cardiovascular Center-type ventricular assist system: (A) pediatric (right) and adult (left)-sized blood pumps; (B) standard (left) and compact (right) control-drive units.

agulant is needed when the bypass flow is maintained at greater than 2.0 L/min in the adult-sized pump and 0.8 L/min in the pediatric one [14, 16]. The bypass flow was measured continuously by an electromagnetic flow probe fitted on an outlet conduit. There are two types of control-drive unit (CDU): the standard type with two regular and two backup drivers, and the compact one with one regular driver and one backup driver. The main part of the CDU consists of an automatic electrocardio-

gram synchronization system and an automatic bypass flow control system based on automatic level control of left atrial pressure and flow, in which bypass flow can be altered closely following changes in cardiac function [17]. Two types of CDU are shown in Figure 1. The latest versions of both types of CDU are applicable as the driver for intraaortic balloon pumping and permit 30 minutes of pumping by a built-in compressor and vacuum unit with internal batteries [18].

TOKYO UNIVERSITY-TYPE VAS. The Tokyo University-type VAS was developed at Tokyo University [19]. The blood pump is paracorporeal, pneumatic, and sac-type (Fig 2). The pump and cannulas are made of polyvinyl chloride, and all blood-contacting surfaces are coated with Carbiothane. Two no. 19 Björk-Shiley valves are used as inlet and outlet valves, and an electromagnetic flow probe is placed at the outflow conduit to measure pump output. The stroke volume is 40 mL, and the maximum flow is approximately 5 L/min. This pump is now produced by Nippon Zeon Co Ltd, Tokyo, Japan. The CDU is equipped with a compressor and vacuum pump that can drive two pumps at the same time (see Fig 2). It is capable of functioning in synchronous or asynchronous mode to the electrocardiogram or aortic pressure. Another feature of this CDU is that it has a back-up driver and internal battery packages, which permit 40 minutes of pumping. This CDU is manufactured by Aishin Seiki Co Ltd in Kariya, Aichi, Japan.

Criteria for Use or Removal of Ventricular Assist System

The hemodynamic criteria for profound heart failure are cardiac index less than $2.0 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ in adults and $2.3 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ in pediatric patients, systolic arterial pressure less than 80 mm Hg, left atrial pressure greater than 18 mm Hg for left ventricular failure, and a right atrial pressure greater than 18 mm Hg with a left atrial pressure less than 5 mm Hg for right ventricular failure. The subordinate criteria are urine output less than $0.5 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$, mixed venous oxygen saturation less than 65%, and arteriovenous oxygen difference greater than 7.0 vol%. Clinical impressions are also important. When the circulatory condition stays within these criteria in spite of medical therapy and the use of intraaortic balloon pumping, a left ventricular assist system (LVAS) or a right ventricular assist system (RVAS), or both, was applied.

Criteria for removal of the VAS are a cardiac index greater than $2.5 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ in adults and $2.7 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ in pediatric patients, systolic arterial pressure greater than 100 mm Hg, mixed venous oxygen saturation greater than 65%, and left atrial pressure or right atrial pressure less than 18 mm Hg.

Surgical Techniques for the Implantation of the Ventricular Assist System

The blood pump was installed between the left atrium and the ascending aorta for the LVAS. Cannulation sites of the inlet conduit were the interatrial groove along the

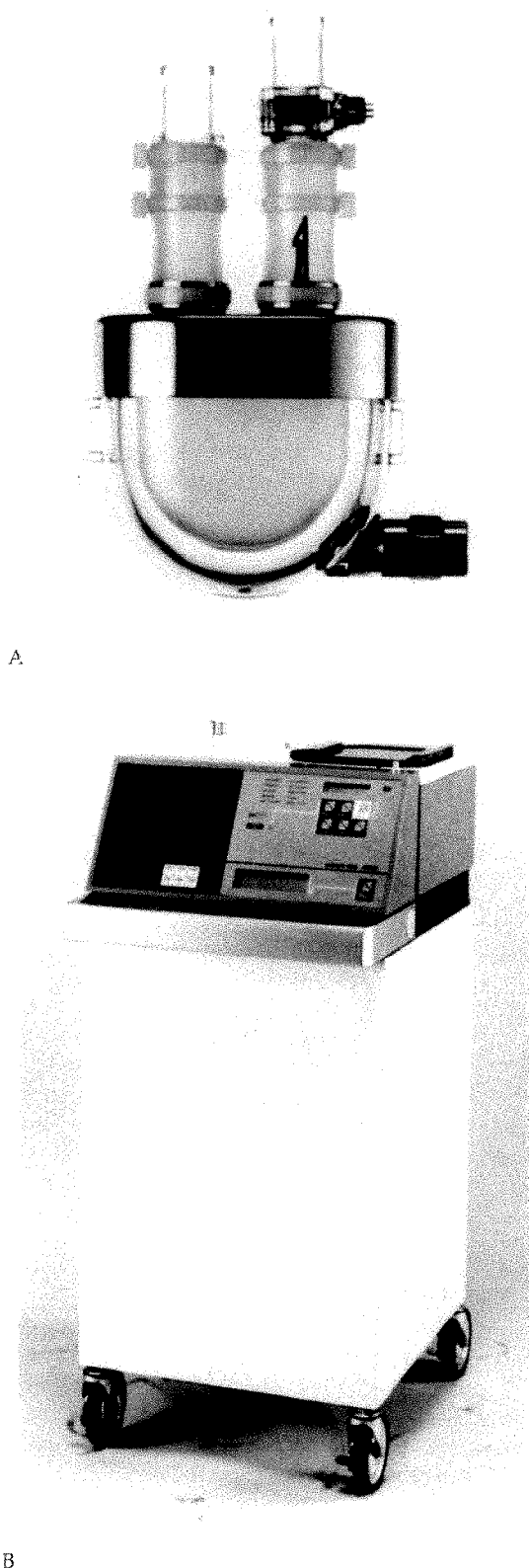


Fig 2. The Tokyo University-type ventricular assist system: (A) blood pump with stroke volume of 40 mL; (B) control-drive unit.

right side of the heart, the left atrial appendage, or the right atrium through the atrial septum. For the RVAS, the blood pump was installed between the right atrium and

Table 1. Duration of Circulatory Support

Variable	No. of Patients	Duration	
		Range	Mean $\pm$ Standard Deviation (d)
Not weaned	101	1 h-70 d	6.7 $\pm$ 12.7
Weaned	101	1 h-25 d	6.8 $\pm$ 4.9
Did not survive	48	4 h-23 d	7.2 $\pm$ 4.9
Survived	53	1 h-25 d	6.4 $\pm$ 4.8
Total	202		6.8 $\pm$ 9.6

the main pulmonary artery. An atrial cuff was used for insertion of the inlet conduit in patients with the NCVC-type VAS.

Patient Profiles

The database of this report as of September 30, 1991, consisted of 202 patients treated with several types of VAS in 41 hospitals in Japan. These included 133 male patients (65.8%) and 69 female patients (34.2%), whose ages ranged from 9 months to 77 years (mean, 54.9 $\pm$ 16.9 years). Adult-sized VASs were applied to 194 patients, whose ages ranged from 13 years to 77 years, and a pediatric-sized one in 8, whose ages ranged from 9 months to 10 years. The indications for application of VAS were failure to be weaned from cardiopulmonary bypass in 147 patients (72.8%), postoperative low cardiac output syndrome in 44 patients (21.8%), and cardiogenic shock without surgical procedure in 11 patients (5.4%).

Results

Types of Device

Five types of device were used: 99 patients (49.0%) were treated with the NCVC-type VAS, 83 (41.1%) with the Tokyo University-type VAS, 14 (6.9%) with the Thomas Giken-type VAS, 3 (1.5%) with the Tohoku University-type VAS, and 3 (1.5%) with the Thoratec-type VAS.

Pump Size and Results

Adult-sized blood pumps were applied to 194 patients; 98 patients (50.5%) were weaned and 53 patients (27.3%) survived. Pediatric-sized blood pumps of the NCVC-type VAS were used in 8 patients; 3 of them (37.5%) were weaned, but none of them survived. The body weight of these patients was between 5.8 and 14 kg.

Duration of Circulatory Support

In the total series of 202 patients, 101 patients (50%) were successfully weaned from the VAS, and 53 patients (26.2%) were long-term survivors who were alive more than 1 month. The duration of circulatory assist had no relation to the results, as shown in Table 1.

Distribution by Year and Results

The first clinical application was performed in 1980 (Fig 3). Between 1986 and 1988, governmental clinical trials of the NCVC-type VAS and the Tokyo University-type VAS were performed and the number of trials reached 153.

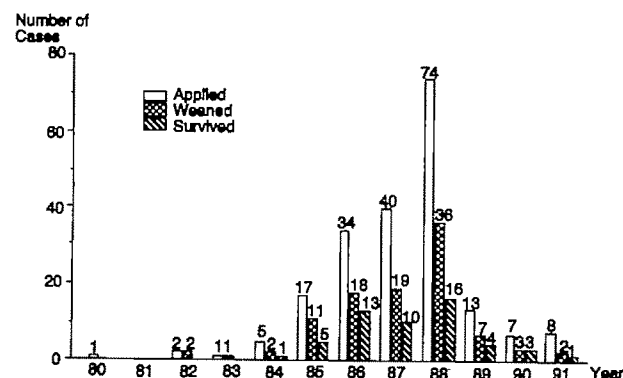


Fig 3. Distribution by year and results (through Sep 30, 1991).

During these clinical trials, the blood pump set was provided free of charge. After the approval, the number of VAS cases decreased, because the cost of these two types of VAS was not covered by medical insurance.

Distribution by Age and Results

Ages of more than 85% of patients ranged from 40 to more than 70 years, whereas there were 7 children (3.5%) less than 10 years old (Fig 4). Thirty patients, or 14.9%, were more than 70 years old, and their results were better than those of the patients between 60 and 70 years old. The patients aged 40 to 50 years had the best clinical results. The mortality of young patients was high.

Primary Diagnoses and Results

Of 202 patients, primary diagnoses were ischemic heart disease in 106 (52.5%), valvular heart disease in 48 (23.8%), and ischemic heart disease with valvular heart disease in 11 (5.4%) (Fig 5). Other diagnoses included congenital heart disease in 19 (9.4%), aortic disease in 11 (5.4%), and miscellaneous diseases in 8 (4.0%). Clinical results in patients with congenital heart disease and aortic disease were worse, and no one survived in the latter group.

Indications for Ventricular Assist System Application and Results

The VAS was applied to 147 patients (72.8%) because they could not be weaned from cardiopulmonary bypass (Fig

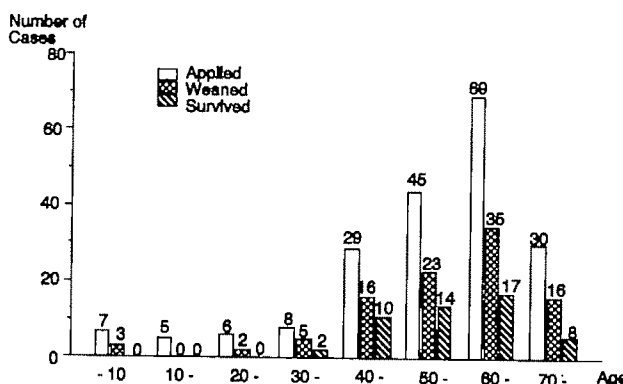


Fig 4. Distribution by age and results (through Sep 30, 1991).

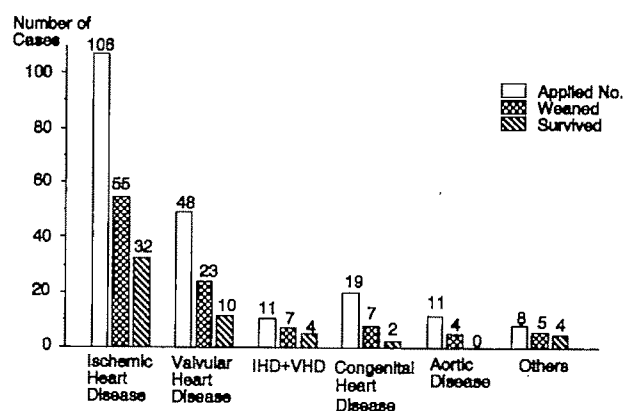


Fig 5. Primary diagnoses and results (through Sep 30, 1991). (IHD = ischemic heart disease; VHD = valvular heart disease.)

6). Forty-four patients required VAS application because of postoperative low cardiac output syndrome. Eleven patients received the VAS because of cardiogenic shock after no surgical procedure was performed. In postcardiotomy patients, the patients with failure to be weaned from cardiopulmonary bypass showed better results than those with postoperative low output syndrome. This may be related to earlier application of VAS in the former. In cardiogenic shock without a surgical procedure, 3 of 11 patients (27.3%) were weaned from the VAS and 2 patients (18.2%) survived.

No patients received a VAS as a bridge to heart transplantation because there is no consent to transplantation with a brain-dead donor in Japan.

Types of Assist and Results

An LVAS has been used for the majority of patients (172 patients; 85.1%) (Fig 7). Another 17 patients (8.4%) received an RVAS, and 13 (6.4%) a biventricular assist system. The results in patients with an RVAS were much better than those in patients with an LVAS. The rate of separation from RVAS and survival rate were excellent. The worst clinical results have been obtained in patients with biventricular assist, which corresponds to the experience in other countries.

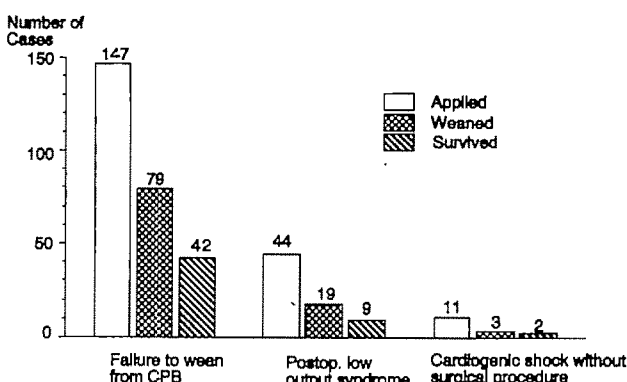


Fig 6. Indications and results (through Sep 30, 1991). (CPB = cardiopulmonary bypass.)

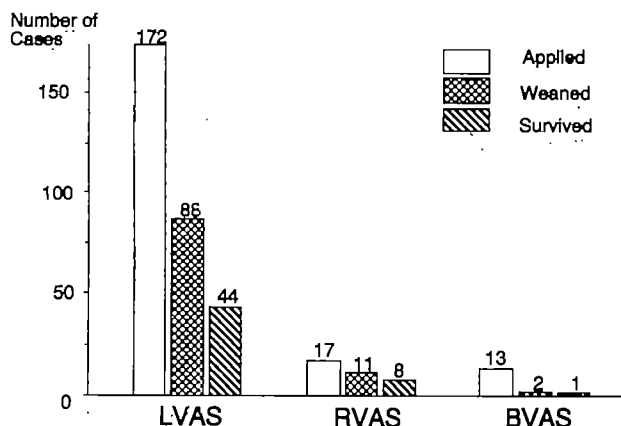


Fig 7. Types of assist and results (through Sep 30, 1991). (BVAS = biventricular assist system; LVAS = left ventricular assist system; RVAS = right ventricular assist system.)

Assisted Duration and Results

The assisted duration of VAS and the corresponding clinical results for 202 patients are shown in Figure 8. The duration ranged from 1 hour to 70 days, and most patients were on the VAS for less than 14 days. Of the 59 patients on the VAS from 3 to 7 days, 46 (78.0%) were weaned and 27 (45.8%) survived. These results are fairly good. The longest support was 70 days, and the longest support in a patient who survived was 25 days. Of those receiving VAS support for less than 1 day, only 9 (18%) were weaned and 5 (10%) survived. The corresponding figures for patients receiving VAS support for more than 14 days were 8 (42.1%) and 3 (15.8%), respectively.

Acute Myocardial Infarction With Cardiogenic Shock

Sixty-three patients with cardiogenic shock after an acute myocardial infarction were treated with a VAS. An LVAS was applied to more than 95% of patients. Diagnoses and procedures are summarized in Table 2. In the group with acute myocardial infarction, 2 of 5 LVAS patients without coronary artery bypass grafting were weaned and 1 survived. In the group with acute myocardial infarction and ventricular septal perforation, the patients with LVAS application with ventricular septal perforation closure

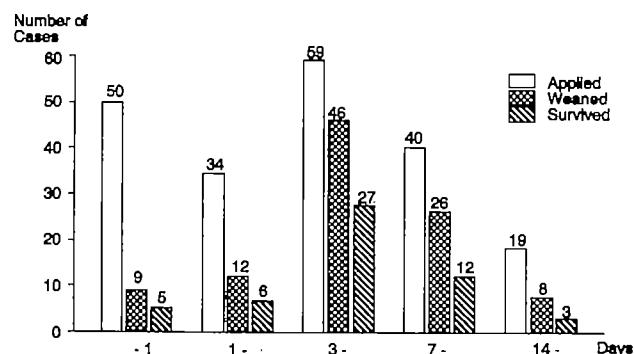


Fig 8. Assisted duration and results (through Sep 30, 1991).

Table 2. Acute Myocardial Infarction With Cardiogenic Shock

Condition	Procedure	No. of Patients	Weaned	Survived
AMI	CABG	26	10 (38.5%)	6 (23.1%)
	No CABG	5	2 (40.0%)	1 (20.0%)
AMI + VSP	Closure	30	19 (63.3%)	9 (30.0%)
	No closure	1	0 (0%)	(0%)
AMI + MR	CABG + MVP	1	1 (100%)	1 (100%)
Total		63	32 (50.8%)	17 (27.0%)

AMI = acute myocardial infarction; CABG = coronary artery bypass grafting; MR = mitral regurgitation; MVP = mitral valve plication; VSP = ventricular septal perforation.

showed a better weaning rate (63.3%) and survival rate (30.0%).

Causes of Death

Major causes of death in nonweaned patients were heart failure, multiple organ failure, and bleeding (Fig 9). After removal of the VAS, they included multiorgan failure and recurrent heart failure.

Postoperative Findings in the Blood Pumps of NCVC Ventricular Assist Systems

Pictures of representative postoperative pumps of the NCVC-type VAS in its clinical trial with 92 patients are shown in Figure 10. In most cases, inside the pump was very clean (see Fig 10A). However, macroscopic ring-shaped thrombus formation was noticed in the groove around the valve (ring-shaped thrombus) in 8 patients in the clinical trial (8.7%) (see Fig 10D). Macroscopic thrombus formation was also noticed inside the pump in 8 (see Fig 10C). Concerning this type of thrombus formation, strong and repeated contact of the diaphragm with the housing might have caused delamination of the absorbed protein layer, resulting in the formation of surface thrombi [15]. Also, spotted white thrombi were noted in the case of sepsis (see Fig 10B). However, pump-

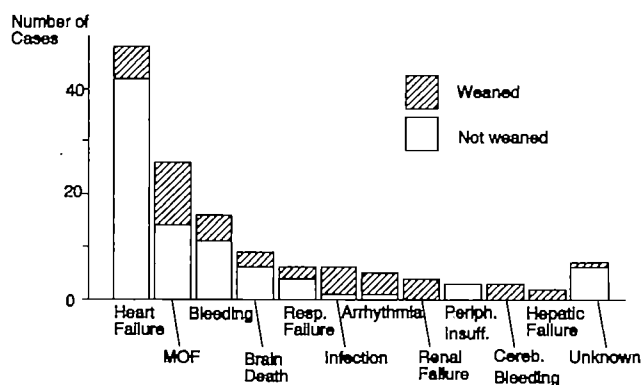


Fig 9. Causes of death (through Sep 30, 1991). (MOF = multiorgan failure.)

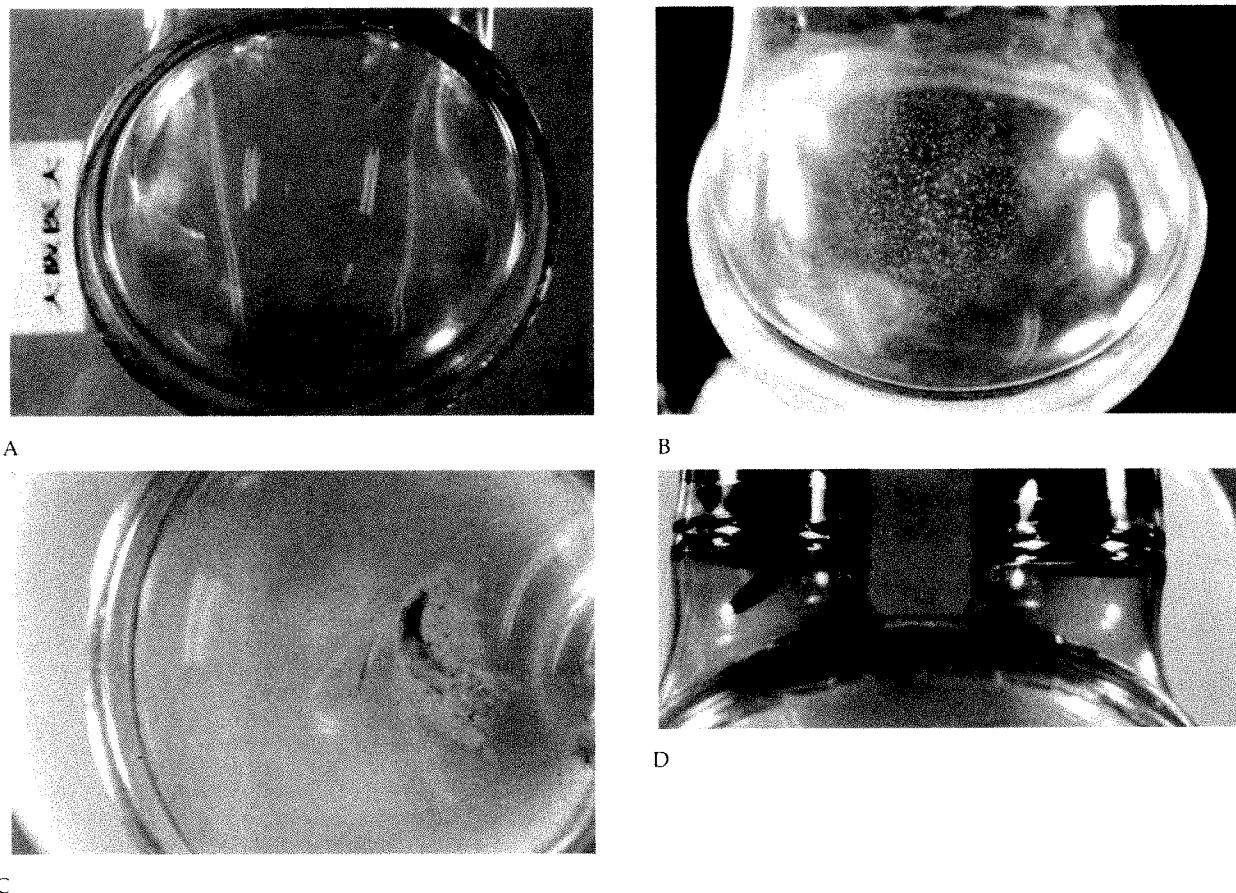


Fig 10. Representative postoperative findings in the NCVC-type ventricular assist system blood pump: (A) No thrombus formation in most cases; (B) spotted white thrombus formation in cases of sepsis; (C) membranous thrombus on the diaphragm; (D) ring-shaped thrombus formation around the valves.

originated serious complications, such as thromboembolism, were not seen.

Comment

The Japanese government has approved two types of VAS, the NCVC type and the Tokyo University type, for commercial release. In the clinical trials, the NCVC-type VAS showed a maximal output of 6.8 L/min in the adult-sized pump and 1.9 L/min in the pediatric one; the mean bypass flow was 4.14 ± 1.04 L/min and 1.43 ± 0.53 L/min, respectively [11]. These pumps had the capacity of substituting for 100% of cardiac function. The Tokyo University-type VAS showed a mean bypass flow of 2.73 ± 0.52 L/min, and the reported limiting factor was the volume to return to the pump [13]. Both pulsatile-type VASs have been proved to be clinically effective, reliable, and durable devices for salvaging a failing heart.

From clinical experience with VASs in Japan, delay of application and heart failure were big concerns for improving the results. The biochemical profiles and microscopic studies of patients with multiorgan failure in whom the NCVC-type VAS was applied indicated that major organs were exposed to prolonged ischemia before VAS application [11, 12]. In patients with heart failure, unre-

coverable heart failure or combined severe right ventricular failure in LVAS was recognized. Because most patients, especially after cardiectomy, had associated right ventricular failure, if an LVAS alone could not maintain the normal circulation with a right atrial pressure greater than 15 mm Hg and catecholamine, an RVAS should have been applied without losing the timing [20]. For unrecoverable heart failure, heart transplantation should have been carried out, but at present it is not in practice in Japan [21]. It should be kept in mind that the decision to use a VAS should not be delayed. It should be applied before major organs, including the heart itself, are irreversibly damaged.

The causes of death in weaned patients included recurrent heart failure and arrhythmia. The timing of removal of VAS was an important factor for improvement of the survival rate. The optimal period of assist varies considerably according to the patient's condition. These two types of VAS allow for long assistance, especially in the NCVC-type VAS (3 months), so a VAS should be removed after sufficient recovery of the failing heart has been realized [22].

In patients with acute myocardial infarction and cardiogenic shock, the weaning rate of patients with LVAS application alone was 40% and the survival rate was 20%,

which corresponds to the result in patients with LVAS application and coronary artery bypass grafting. These results suggest that LVAS application without coronary artery bypass grafting should be considered in the treatment [23, 24]. Among patients with acute myocardial infarction and ventricular septal perforation, half of the weaned patients died. The main cause of death of these patients was multiple organ failure, which was probably caused by the prolonged low cardiac output condition before the procedure. Early surgical procedure with LVAS application should be considered for improvement of the survival rate.

Pulsatile VASs, the NCVC type and the Tokyo University type, have proved to be effective devices for acute profound heart failure including after cardiectomy, and salvage numbers are increasing with improvement in patient selection and early application.

We greatly appreciate the contributions of the members of the investigational hospitals and those in the industry who provided the data in this report.

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External Pulsatile Circulatory Support

Moderator: Charles-Julien Hahn, MD

Panelists: William L. Holman, MD, Jack G. Copeland III, MD, and Gerard Champsaur, MD

MODERATOR HAHN: As the start of this session is already delayed, I will try to save some time by asking Dr Holman to give his presentation without preliminary comments.

DR HOLMAN: My talk will concern our experience with an external pulsatile assist device manufactured by Thoratec, Inc. We have had other experiences with the Thermo Cardiosystems device, but it is an *internal* pulsatile assist device. Today I will concentrate only on the Thoratec pump. It is well known that this mechanical circulatory support system is made of an external hard polysulfone shell and a segmented polyurethane pumping sac. Two Björk-Shiley disk valves are placed at the inlet and outlet of the sac, and polyurethane cannulas connect the heart and the great vessels to the device.

One of the problems we had to face, as already mentioned by other speakers, is bleeding at the time of implantation. Especially when patients already have a bleeding diathesis, persistent hemorrhage at the time of operation is not uncommon. Most of our pretransplantation patients are given warfarin sodium to minimize pulmonary thromboembolism. Moreover, these patients often have elevated pressure on the right side of the heart with hepatic congestion and a high prothrombin time. Because of all the blood product transfusions used to control bleeding, we noted that 2 of our 10 patients developed an elevated panel reactive antibody (PRA) titer that at times became quite high. One patient's PRA peaked at 62%. Another patient's PRA was as high as 40%. When the PRA is elevated, it becomes difficult to find a cross-match-negative donor heart. We are now giving as many transfusions as possible through leukocyte filters to minimize the patient's exposure to foreign HLA antigens.

Other solutions to the PRA problem may come from using plasmapheresis to decrease the PRA titer. However, the efficacy of plasmapheresis to decrease the PRA titer has not yet been proved. We used plasmapheresis in one young woman with postpartum cardiomyopathy. She had arrhythmias including episodes of ventricular fibrillation during which flow in the device dropped down to 3 to 4 L/min. This situation was not acceptable for long-term support; therefore, we used plasmapheresis to decrease her PRA titer.

Another patient was doing well on the ventricular assist device and his PRA titer slowly decreased over time. As noted by other institutions, the PRA titer will usually decrease over time.

In long-term circulatory support, anticoagulation is important to prevent clot formation. It is also important to avoid any kinking or pressure on the polyurethane cannulas.

The Thoratec device can cause a low level of on-going hemolysis, with a plasma free hemoglobin level in the range of 5 to 15 mg/dL. Occasionally there is also a decrease in the hematocrit. If the hematocrit is less than 0.20, a transfusion of erythrocytes is usually given. This entails a risk of increasing the PRA titer.

After 3 or 4 weeks of circulatory assist, inflammatory tissue surrounds the heart. We have faced the problem of inflammatory tissue and adhesions in a 19-year-old man who had acute myocarditis. His heart recovered during the period of circulatory assist, and we were able to remove the cannulas of the ventricular assist device without too many problems. But in another patient (let me remind you, these patients are anticoagulated) at the time of cardiac transplantation disseminated intravascular coagulopathy developed and the patient bled to death.

In one pump we found a rim of white thrombus on the mechanical valve. This happened to be a right-sided pump in a patient who had recovery of right heart function after implantation of the pump. Because the pump is heterotopic, there is some competition with the natural ventricle. When the ventricle is in severe failure, most of the blood goes to the pump. But when the heart starts to recover, the pump may not fill as well. This is another reason why anticoagulation is important (prevention of embolism). Any type of pump, if used a long time in a substantial number of patients, will generate thromboembolic complications. A computed tomographic scan of a patient who was assisted during 193 days showed what must have been a septic embolus that made such a neurologic deficit that the pump was discontinued at the family's request.

Cerebral thromboembolism will occur despite the best anticoagulation. We routinely use warfarin sodium after a week. Is it enough? The question is not yet solved.

We had no fixed neurologic deficits in patients with a Thoratec device for periods less than 70 or 80 days. We had one splenic infarct and one transient ischemic attack after 70 days but with a normal computed tomographic scan and a normal neurological examination.

For longer periods of assistance—160 to 190 days—we had some fixed neurologic deficits. In 1 patient we found vegetations in the Dacron conduit with cultures of the blood positive for *Candida*. This patient was treated with amphotericin B for 6 weeks and became afebrile. The white blood cell count was normal and the cultures were sterile, but the pathologist still found organisms hiding

inside the vegetations. I am fairly certain that the cerebral embolus came from this vegetation.

Early infections were very rare with this device, even if it is not statistically validated. When yeast infection occurs, however, it may be an unsolvable problem. It appears that the *Candida* homes in on the Dacron graft, its initial source being from the gastrointestinal tract, especially the oropharynx and esophagus. This is the reason why we adopted Bob Kormos' protocol (University of Pittsburgh): nystatin at the drop of a hat for prolonged periods.

We had, as an unusual complication, a rupture of an outflow cannula, a kind of slow tear that happened after 90 days of support with a ventricular assist device. This patient had a transient ischemic attack; 4 hours later computed tomography was performed, but when he was put on the gantry it was noted that some blood was leaking out of the cannula going to the inflow of the pump. It was, of course, 1 o'clock on a Sunday morning! So we had no choice but to take the patient back to the operating room and remove the ventricular assist device from the apex, put a cannula in the left atrium, and change the aortic graft. The patient left the hospital in good condition. We were looking with the company at possible changes that could happen in the polyurethane or in the wire wrap that runs right up to the edge of the teflon. The tear could be related to the use of peroxide or the povidone-iodine. It may be that the povidone-iodine impregnates the tin solder at the end of the wire and forms an iodide that is a little weaker, giving the possibility for the wire to pop under stress or for some other reasons. The unsoldered wire can unwind and slice through the polyurethane.

To avoid the problem of adhesions, we are using a sheet of Gore-Tex covering the cannulas and the heart underneath the sternum. As the Dacron is attracted to the middle part of the sternum, like a magnet, this sheet keeps the Dacron away so that, when the sternum is reopened with an oscillating saw, there is virtually no chance to get in the Dacron. As an example, after 90 days, the sheet of Gore-Tex could be peeled easily off the heart. As the sheet covers the atrium all the way down to the pulmonary veins, the dissection is done in case a bypass must be quickly installed.

MODERATOR HAHN: Thank you very much, Dr Holman, for this interesting experience with the Thoratec device. Now I should like to ask Dr Champsaur from Lyon to bring the experience of the Institute of Cardiology of Lyon.

DR CHAMPSAUR: In the cardiovascular hospital in Lyon we have supported 18 patients using the Abiomed 5000 system from January 1988 to July 1991. The age ranged from 7 years to 58 years, and the weight from 20 to 90 kg.

Presupport diagnoses were as usual: idiopathic cardiomyopathy in 11 patients and ischemic cardiomyopathy in 3 (2 with acute myocardial infarctions). Two patients had acute graft rejection, and in 2 other patients the device

was implanted 48 hours after a previous cardiac operation. Five patients experienced a cardiac arrest: 1 or more immediately before implantation. Biventricular support was necessary in 17 patients, and a single left support was used in only 1 patient. The bypass was routinely implanted in the periphery and cannulation was as usual using the intraatrial groove, right atrial appendage, the ascending aorta, and the main pulmonary artery for the outflow cannula. The protamine was reversed after coming off bypass and continuous heparin infusion was started when the activated clotting time was found to be less than 140 seconds. It was then slowly adjusted to remain between 150 and 200 seconds. The range of duration for support was between 1 and 11 days, with a mean of 5.5 days.

Some complications have been observed during this period of support, namely, bleeding complications leading to a reoperation in 4 patients, transient neurological deficit in 1 patient, persistent renal failure leading to renal dialysis in 1 patient, and persistent hypothermia in the early patients who we observed. There were, however, no instances of documented infection, pump failure, or thrombosis in the pumps. One death occurred during support on the ninth day owing to undiagnosed chest clotting and tamponade. Seventeen of 18 patients underwent transplantation, and we observed six early deaths within 30 days after transplantation: 2 due to graft failure, 2 due to persistent multiorgan failure, 1 due to delayed tamponade, and 1 due to septic shock. One death occurred on the second month after operation and was caused by cytomegalovirus pneumonia in a patient after acute rejection.

To summarize our experience in this small series, there were 18 patients supported; 17 underwent transplantation. There were six early deaths and one late death after transplantation. And finally, 10 patients were discharged from the hospital and followed up for 8 months to 2.5 years. This device in this experience has been shown to be a safe cardiac support system with no mechanical failure so far and no serious hemolysis; the mean plasma free hemoglobin level remained less than 2 mg/dL, and thanks to the design of the precoated outflow cannula the blood loss now can be reduced. It is an efficient system and it has the ability to restore and sustain circulation in mortally ill patients as shown by the usual parameters. Noteworthy is the fact that normal hemodynamics were maintained in 2 patients experiencing ventricular tachycardia for more than 12 hours, 1 of them being a patient on a single left ventricular support. As we have seen, the system has some limits. As for other external ventricles, those external ventricles would limit the use for an extended duration, although there have been some, as we have recently heard, in long-term support with external ventricles. In this particular case the pump is over-sized for pediatric support.

MODERATOR HAHN: Thank you, Dr Champsaur. Let me first ask the audience if there are some questions.

DR GESLIP (Berlin, Germany): I want to ask Dr Champ-saur, how could you manage after an average pumping time of 5.5 days to get a heart for transplantation? We were never able to do it in such a short time.

DR CHAMPSAUR: This afternoon, we heard another experience from Berlin; they were able to get hearts in a much shorter time than we do. In France, actually, we can have hearts in a few days, as I mentioned, despite the fact that we are starting to observe a donor shortage. This is why we can expect a limitation of this procedure in the future.

MODERATOR HAHN: I would like to make a comment on the cannulation of these different devices. When dealing with extremely sick patients at the real end of their cardiac failure, the fragility of the cardiac cavities is such that we can get dramatic accidents, mainly with the cannulation of the left atrium. I saw that Dr Copeland is putting in the cannulas almost the same way as we did in our series of 35 patients using the Pierce-Donachy device made by Thoratec. Doctor Copeland, where do you put the left atrial cannula?

DR COPELAND: We put the cannula in the interatrial groove just anterior to and perhaps caudal to the superior pulmonary vein, so that we do not compromise the superior pulmonary vein but we know for sure the cannula is in the left atrium.

MODERATOR HAHN: And do you keep your cannula in the atrium or do you put it in the left ventricle?

DR COPELAND: We have tended to keep it in the atrium. We have noted that the exact angulation of the cannula makes a tremendous amount of difference, and on one occasion we have reopened the chest in the operating room to reposition the cannula slightly and change the output by probably 50%. So we think that is a very important part of the operation. A fair amount of attention and fiddling around, I think, needs to take place if you are going to use atrial cannulation.

MODERATOR HAHN: This is exactly what we were doing because it could be such a source of mistakes. The cannulation of the left atrium in these kind of patients is really a major technical problem, and the way Dr Copeland explained how he is putting in this cannula is the safest one, because the tissue in the groove is very good. It does not have the fragility of the rest of the left atrium. We made quite a number of mistakes in the beginning by trying to put cannulas through the appendage or through the apex of the left ventricle.

Most of the patients you showed us were bridged to transplantation with biventricular assist devices, but what about the univentricular device? Did you try, Dr Holman, to assist patients in a nonirreversible heart failure? And what did you do for this kind of patient?

DR HOLMAN: I think that is an important point to discuss when you are making a decision about which type of cannulation technique to use. Assuming that your device gives you a few options, you have to think about the future of the patient. I have had to remove one pump from the apex of the ventricle, and it is a fairly daunting challenge, not so much to get it out but to reconstruct the ventricle with the jagged, torn-up edge that is left. Atrial cannulation has tremendous benefit if you think there is any chance that the heart might recover function. The one patient who I was discussing earlier with Dr Hahn was a 19-year-old who came in with acute decompensation and what we presume was acute myocarditis. My cardiologist actually convinced me to use atrial cannulation. I thought that we would get better flows, which you typically do, using apical cannulation. He said, "Now look, give him a chance. His cardiac index right now is only $1.4 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ on all these medications and so forth. However, if it is myocarditis and he does improve, we want to take the device out." After about 4 weeks on the ventricular assist device the patient began to show signs of cardiac recovery. The only reason that patient did not receive a transplant was that there was no donor heart available during that time. But his heart went on to recover completely, and the actual explantation of the atrial cannulation was fairly straightforward. So this is an important consideration. I think that you really have to think about it carefully before you put in the device.

Another difficult problem is a patient with a prosthetic valve. But if you think patients are going to fibrillate then you are really forced to go to apical cannulation, because they can fibrillate for a period of time, and stasis thrombosis can develop in the ventricle; if they spontaneously defibrillate they can eject a large amount of thrombus into their bloodstream, and then your superior support is over. I would like to ask the other two surgeons, what would you do with a patient who has a prosthetic aortic valve in place? With good ventricular assist device support that valve is going to be totally closed for extended periods and a large thrombus will develop despite anticoagulation. How would you handle that patient, Dr Champsaur and Dr Copeland?

DR COPELAND: I am not sure. I think that if we were forced into the situation, our tendency would be to run at the lowest output that kept the patient alive and make sure that the valve opened. I think we would anticoagulate the patient as we normally do and hopefully get the device out as early as possible. I think that is a tough situation.

DR CHAMPSAUR: We had this situation in an old woman who had double-valve replacement and was 1 of the 2 patients who was a so-called postcardiotomy patient in our experience. She was on the device for 11 days but there was no thrombosis at the time of explantation and transplantation.

SPEAKER: We supported a 20-year-old nurse about 2 weeks ago who had an urgent aortic valve replacement

and could not be weaned. We supported her with an apical Thoratec ventricular assist device and her heart would not beat at all. We anticoagulated her. She had a St. Jude aortic valve, and we took the first heart available. That took about 2 weeks. At the time of transplantation the aortic valve was absolutely frozen. She had been on anticoagulants including heparin the entire time. The aortic valve could not be forcibly opened with a finger, it was thrombosed so heavily. So I think the answer is to perform transplantation as soon as possible. Some protocols, as a matter of fact, including, I think, Novacor's, indicate that a mechanical valve would be a contraindication to use one of these systems. But we just could not turn down a 20-year-old woman and so we did it.

Could I ask Jack Copeland one other question? He showed those slides showing the transillumination and those little white dots, I guess he called them, which I assume are platelet thrombi. That was sort of fascinating to me because I do not know that we have looked for them but maybe they would have been there in our devices. I wonder if you could use aspirin therapy or dipyridamole or anything else to alter that pattern. How would you plan to deal with that in the future?

DR COPELAND: You know, I think the more I hear about aspirin therapy the more intrigued I am by it. The TCI experience with 50 patients and only one embolus related to the cannula—not to the device—makes you wonder if aspirin is useful. We have been sort of reticent to use aspirin in these patients because we are always thinking ahead to the time of the transplant operation, when having aspirin on board may make things quite difficult. But I agree with your point that perhaps aspirin is a good idea. These are platelet thrombi. There is no doubt about it. We have looked at them microscopically and with scanning electron microscopy and so forth. One of the things that I am going to take back from this meeting is to be a little more aggressive with the use of aspirin.

MODERATOR HAHN: Don't you think that it is coming from the type of biomaterial you use?

DR COPELAND: I do not think it is necessarily related to biomaterial. I think it is more related, at least as we

have mapped these things, to flow patterns within the device. We have found, for instance, if we mobilize the patients early and get them in a vertical position we do not get an uneven filling pattern into the device so that the diaphragm moves symmetrically and we tend not to get deposition of these things. So another item, I think, that is pretty high on our list is mobilizing the patients, getting the patients into the most advantageous physical position to minimize the low-flow areas within the device.

MODERATOR HAHN: About the Thoratec device, we saw an enormous difference in the first series of patients operated on, with this kind of small clots in the sac of the device, and the last series, in which we did not see that anymore, because the polyurethane was changed. It was more hemocompatible than the first ones. There must be something about the technical way the sac is made. In your experience with the Thoratec, what is your opinion, Dr Holman?

DR HOLMAN: When we were approved to use the device they had already moved on to the newer segmented polyurethane, but I have never seen a thrombus formation. That is one problem that we have not had. I should never say never, but at least in our explantation photographs for the Food and Drug Administration we have not, as of this date, noted any platelet deposits in the pumping sac. But let me add from our study of these devices that the segmented polyurethane, when it is wet, is an extremely slick substance. You wonder intuitively how platelet deposit or red thrombus would stay on there very long with an actively moving sac and a bloodstream flow. It points up one of the weaknesses in all studies, which I think are inherent to any clinical study in humans. You will never really know what the incidence of thromboembolism is because a lot of these small aggregates will go out and be clinically undetectable; in fact, unless you do an autopsy that borders on virtually impossible compulsion, you will never see them either. So what we are really counting are clinically evident, and for the most part that is neurologic complications from thromboembolism. The short answer to your question is no, we have not yet seen any aggregates on the biomer.

Internal Pulsatile Circulatory Support

Moderator: Peer M. Portner, PhD

Panelists: William A. Baumgartner, MD, Christian Cabrol, MD, and O. H. Frazier, MD

MODERATOR PORTNER: We are most fortunate to have with us, on the panel, three internationally known experts with a considerable collective clinical experience in implanted pulsatile circulatory support systems. Doctor Christian Cabrol from Hôpital la Pitié in Paris will talk about the Symbion J7 (Jarvik) artificial heart experience. Then Dr O. H. Frazier from the Texas Heart Institute and Dr William Baumgartner from Johns Hopkins will discuss the TCI and Novacor left ventricular assist systems.

The primary purpose of these sessions is to provide a forum to address the practical issues associated with the clinical use of implantable devices. This will only be achieved if there is a dialogue with you, so I encourage your participation. We shall start with a short presentation from each of the panelists. When the program was put together, a videotape was anticipated from Symbion describing the J7 device. The subsequent demise of Symbion left a gap in the video program, and so I have asked Dr Cabrol if he would take that into consideration in his presentation. He will be followed by Drs Frazier and Baumgartner and then comments from the audience.

DR CABROL: Doctor Portner, ladies and gentlemen, I am very happy and very proud to be invited to such an interesting meeting. As Dr Portner said, I will present our experience on the use of the total artificial heart, Jarvik 7. Our experience is based on 58 patients and the implant duration is from 1 to 623 days. Our total experience with this device is more than 1,400 days. As you know, the Jarvik 7 total artificial heart is placed in the pericardial cavity after excision of both ventricles as in conventional heart transplantation. There is a left and right ventricle for each artificial heart. They are connected by drive lines through the skin to an external console. Each ventricle is made of a rigid shell divided into two chambers by a flexible diaphragm. In the blood chamber, blood enters from the atrium through an artificial inflow valve (Medtronic-Hall) and leaves the chamber through an outflow valve to the pulmonary artery or the aorta. The other (air) chamber is connected by a drive line to the external console. The device works on a complete empty mode in each systole.

The implant operation is performed using the usual midline vertical sternotomy. The heart is exposed through the usual incision of the pericardium and conventional cardiopulmonary bypass is set up between the venae cavae and ascending aorta. The heart is excised, leaving as much as possible of aorta and pulmonary artery. On the atrial side, in contrast to transplantation, as much atrium

as possible is left, by transecting the ventricle side of the atrioventricular orifice and excising the tricuspid and mitral valves while leaving enough solid tissue to suture to the device cuff. A running suture is used, usually 4-0 Prolene for the atria and 5-0 Prolene for the pulmonary artery and aorta. Each suture line is inspected to ensure that there is no leak. The left ventricle is connected with the so-called quick-connect made of a Silastic ring; first the atrial connection, then the aortic connection. After that the right ventricle is attached, first at the tricuspid connection and then the pulmonary artery connection. There are two models, one with 100-mL blood chambers, for large patients, and a smaller 70-mL model, which is the model usually used. After placement of the ventricles they are carefully deaired through special deairing buttons. The ventricles are then connected to the console and we calculate the output. For the 70-mL heart the stroke volume is usually 50 mL. So we set up a rate of 100 beats/min, which gives a cardiac output of 5 L/min. Then cardiopulmonary bypass is progressively weaned and the operation completed in the usual way. The drive lines are placed through special skin orifices using a device that permits some motion but avoids the possibility for bacteria to go up the line. There are console control buttons for both right and left ventricles and a spare device in case of problems.

We set the systolic driving pressure of the right ventricle usually to 50 mm Hg, or a little more, the left ventricle usually to 200 mm Hg, the heart rate and the systole/diastole percentage. The different alarms, including output and pumping rate, are also set. A computer controls device operation, showing different curves, like the ventricle filling curves. There is usually a higher output on the left side because of the shunt between the right and the left circulation through the lungs. The filling curve of each artificial ventricle is a velocity curve. Blood enters very rapidly at the beginning of diastole, then more slowly, and the ventricle is never completely filled. This allows for a Starling effect when venous pressure increases. So you can follow the filling of the ventricle, which is very important, but you can also have an idea of the systemic blood volume. The typical curve of a hypervolemic patient is higher than in a hypovolemic patient. So you can correct for this anomaly. It is also possible to look at the filling curve and differentiate normal filling of the right ventricle from very abnormal filling due to compression of the venae cavae by the right ventricle. It is mandatory to reoperate to correct this compression. It is also possible to observe the ejection curve, which is very similar to normal ventricular ejection, with isometric contraction and blood ejection phases. With each beat the

ventricle completes systole with a typical signature of the empty point. In diastole, this curve allows a measure of the systemic vascular resistance. If the curve increases slowly, there is a high systemic vascular resistance indicating the use of vasodilator drugs. Finally, the computer also gives the average cardiac output for each three beats.

The main problem in using this device is infection because of the large amount of foreign material behind the sternum. In our series, this has not been a problem. The second problem is the coagulation. I will discuss this in more detail this afternoon, but I can say that we use a different approach. We have observed that the total artificial heart modifies all coagulation factors. The conventional tests usually do not reflect the perturbation of the coagulation processes. Platelet activity is usually accentuated, there is excess thrombin formation, and there is hyperfibrinolysis. The problem is not to put these patients on an "anticoagulation status" but on a "normal coagulation status," decreasing platelet activity to normal with dipyridamole and then aspirin, giving heparin to compensate the excess thrombin formation, and using aprotinin to stop hyperfibrinolysis. High doses of dipyridamole are used—about 300 mg every 6 hours—and then aspirin at 50 mg a day. To control thrombin formation, small doses of heparin between 10 and 50 mg a day are given intravenously to stop hyperfibrinolysis, and aprotinin is used on the first day at a dose of 1 million units.

Another goal is to have immediate good hemodynamics—a normal cardiac output and normal systemic arterial pressures. Patients are often hypertensive, so we have to use systemic vasodilators. Right atrial pressure is often elevated by device compression of the venae cavae, and must be decreased to avoid impairment of kidney and liver function. It is essential to follow this with the control curves, especially the filling curves. In our experience, after a few hours, there was a minimal manipulation of control parameters and a moderate use of drugs. Finally, we are very pleased with this device, and are still using it in selected indications. We know it very well. It is a simple and safe device and it allows us to wait until transplantation can be done with the patient in an adequate condition. That means when everything is normal, and not in an emergency, so that survival after transplantation, in our experience, has been at least equal to survival after conventional orthotopic transplantation.

MODERATOR PORTNER: Thank you, Dr Cabrol. Doctor Frazier?

DR FRAZIER: Thank you, Dr Portner. I wanted to provide a little more detail about the implantation techniques for the Thermo Cardiosystems internal, pulsatile blood pump, as well as patient management techniques.

We began performing animal research on this pump in the early 1980s. The pump used then was basically the same pump that we are now using clinically, except that the inlet cannula has been considerably shortened in the clinical model. As many of you know, one of the distinguishing characteristics of this pump is the textured blood-contacting surface, which promotes incorporation

of red blood cells, eventually resulting in identifiable endothelial cell growth on the flexing surface of the device.

The first time I used this pump, I placed it extraperitoneally, but this dissection resulted in the development of a large hematoma. Since then, I have placed the pump intraperitoneally; it fits well in the left upper quadrant, anterior to the spleen and to the stomach. The pump is implanted while the patient is on total cardiopulmonary bypass, and the heart is arrested. I like to cannulate the aorta for arterial inflow, but this can also be accomplished through the groin. The midline incision should be extended to the umbilicus to provide an opening large enough to insert the pump. The device is powered by a simple air-driven console. The drive line, which is connected to the console, exits the body anterior to the left superior iliac spine.

When the system is activated, air may be sucked into the inlet tube, so time and patience are necessary in filling the pump to ensure that all the air is removed. Recently, we have also preclotted the inlet side of the graft, and this seems to decrease the problem. Although the pump is big, it fit in a 54-kg man, who was able to eat and to walk without problems. We also like to ensure that the inlet graft is straight, avoiding any angulation, so that it is directed toward the mitral valve. At first, we worried about bleeding from the cannulation site and spent time reinforcing it with extra pledged sutures. We have not seen bleeding from this area, probably because the left ventricle is decompressed, which minimizes stress on the suture line. Finally, we use transesophageal echocardiography intraoperatively to ensure that the inlet cannula is properly positioned.

After completing insertion of the inlet cannula, the distal end of the outlet graft is sewn to the aorta, and the proximal end is connected to the pump. Care is taken to ensure that an adequate length has been obtained. The length can be adjusted by excising an appropriate length and performing a graft-to-graft anastomosis. Patience is necessary to ensure that all of the air is removed from the pump.

After pump function stabilizes, the drive line is exteriorized. The drive line has been well tolerated, and we have seen no clinically significant complications related to externalization of the drive line.

Postoperative roentgenograms of the patients illustrate the markedly decreased dimensions of the heart, compared with preoperative roentgenograms. It is very important to keep the inlet cannula straight as, because of the diastolic flow, any angulation could promote pannus formation. We have seen this complication in 1 patient.

One of the benefits of intraabdominal placement is that a smooth capsule of fibrous tissue forms around the pump, much like the capsule formed around pacemakers. Within 3 weeks of implantation, the pump becomes well encapsulated, and this may diminish the risk of infections. We have seen no infections of the pump.

If at the time of transplantation excessive bleeding is encountered, the pump can be left in place. The donor heart can be sewn in and the skin closed. When the

coagulation parameters have been corrected and bleeding controlled, the pump can be removed. In general, however, we remove the pump at the time of transplantation.

MODERATOR PORTNER: Thank you, Dr Frazier. Doctor Baumgartner?

DR BAUMGARTNER: Thank you, Dr Portner. I have prepared something similar to what Dr Frazier has presented. Actually there are many technical aspects that Dr Frazier has gone over that apply to both Novacor and TCI implantation.

I thought I would pick some steps important in the implantation process. The first is anastomosis of the outflow graft to the ascending aorta. This is done at the lowest position possible on the aorta. After this, the clamp is moved to the graft. The suture line is then tested for hemostasis, usually after creation of the pump pocket. In most of the Novacor implantations the pump pocket is made anterior to the posterior rectus sheath, somewhat different than the intraabdominal approach described by Dr Frazier for the TCI device. This is usually done before bypass. I will talk about preclotting the graft in a minute. Having completed the aortic anastomosis, connections are then made to the pump/drive unit itself. The drive line exits in the right lower quadrant, superior to the anterior iliac spine. One of the technical points in the implantation is to position the outflow graft somewhat into the right chest, which may require releasing some of the diaphragmatic attachments to the costal margin. This will facilitate reoperation when the median sternotomy incision is reopened. Cannulation of the apex of the ventricle is similar to what has been mentioned already. Pledged sutures are placed around the apex. An important aspect is to check for ventricular thrombus, once you core-out the apex and before insertion of the inflow cannulas.

We centrally cannulate in the majority of patients. Placement of two cannulas allows you to look for a patent foramen. As you have seen from some of the earlier presentations, there have been problems with a patent foramen, especially because decompression, obtained on the left side of the heart with the Novacor device, creates very low left ventricular end-diastolic pressures, occasionally in the negative numbers. With a patent foramen ovale (PFO), the right ventricle and right atrial pressure can be higher than the left and therefore create a shunt from right to left. Finally, deairing is extremely important. We start by filling the pump with saline solution through the inflow conduit, before placement in the left ventricular apex. Then we aspirate air from the inflow graft, the left ventricle, and the outflow graft.

One of the major problems with implantation of all devices has been bleeding. The outflow graft has been a particular source of problems. The primary method of preclotting consists of either blood or fresh frozen plasma, thrombin, and cryoprecipitate, repeated three times. The current outflow graft cannot be autoclaved because of the valve housing. Novacor is developing a valved conduit that can be autoclaved. Another technical method would be to cut the outflow graft at its attachment to the

housing, autoclave the graft, and then reattach it. Perhaps a more simplistic explanation for bleeding through the outflow graft is related to the pressure generated in the graft by pump ejection during deairing. In some cases this may force preclot through the graft interstices. This may be a possible mechanism because good graft hemostasis is usually obtained before cardiopulmonary bypass and deairing. It should also be noted that we are usually dealing with a patient who has an element of liver failure with the added effects of cardiopulmonary bypass.

Explantation is fairly straightforward. If the outflow graft anastomosis occupies most of a short aorta, the groin can be cannulated for arterial inflow. After pump removal a large Hemovac is placed to drain the empty pocket.

Probably the biggest advantage of the internal pulsatile device is the ability to mobilize the patient. It has clearly resulted in transplantation patients who are better candidates than before the device was placed.

MODERATOR PORTNER: Thank you, Dr Baumgartner. Perhaps I could begin the discussion by asking the panelists for comments on device selection. How do you decide whether a patient has adequate right heart function for univentricular left heart support? Or conversely, when do you need concomitant mechanical support of the right ventricle?

DR FRAZIER: Well, we have had 2 patients in whom the Bio-Medicus pump was used for right ventricular support, and we were able to wean both patients from the Bio-Medicus pump. This problem underscores the importance of patient selection, which is the most important criterion for clinically successful use of this technology. A patient with elevated pulmonary resistance is at risk for right ventricular overload. The most desirable patients to undergo HeartMate implantation are those whose condition deteriorates as they await transplantation. Ideally, heart failure should have been present for at least 3 months to allow for preconditioning of the right ventricle. We have been giving prostaglandins preoperatively to many patients with high resistance, and this therapy has been helpful in weaning them from bypass.

DR BAUMGARTNER: I think it is actually fairly obvious in the operating room when you are going to need right heart assist. You are unable to fill the device and concomitantly observe a poorly contracting right ventricle. The administration of multiple blood products often causes pulmonary hypertension requiring increased inotropic support. Once again, bleeding is the major complication of this procedure. Perhaps, if we can reduce the bleeding several of these other problems may be less prevalent.

MODERATOR PORTNER: Doctor Cabrol, how would you choose between the total artificial heart and ventricular assist?

DR CABROL: Well, first of all I say the best device is the device you are acquainted with. You can choose any

device you want, but know it very well and do not change from one device to another. In our own experience, we are using the total artificial heart for some specific indications. In a patient with a massive myocardial infarction with septal rupture that is not easily repaired it is of course very easy to replace the heart with an artificial heart. Another indication is when we do not expect heart recovery. In such a case, we prefer the total artificial heart except in a small patient. Then we use an assist device (external or internal), usually the Nippon-Zeon device because it is a very simple device and has many interesting features. It can be run like an intraaortic balloon pump and the nurses can easily use it without any problems. We are interested now, of course, in using the internal device because of the potential for chronic implantation which will be a very interesting application. We have, since last year, a Novacor device and hope to have, in the very near future, the possibility to use the almost totally implantable left ventricular assist device.

MODERATOR PORTNER: Are there questions from the audience? While people are thinking about questions, Dr Frazier, have you had experience with ventricular fibrillation in any of your patients? And what happens?

DR FRAZIER: We have had 2 patients who experienced fibrillation after the pump had been implanted. One of the pumps had been in for 24 hours and the other, for 36 hours. At the point that fibrillation occurred, the patients had recovered from the pulmonary hypertension associated with cardiopulmonary bypass. The pump kept working, although the flows were reduced. Thus, the real key to overcoming right ventricular failure is maintaining low pulmonary vascular resistance. I will never forget (and Jack Norman is here, and he remembers well) the case of a patient in 1978 who had a stone heart. There was no ventricular function at all. The only thing we had was the intraabdominal left ventricular assist device, which we implanted. The patient was a young man with low pulmonary vascular resistance and he was sustained for 5 days without any right ventricular function.

DR BAUMGARTNER: We have had 1 patient who had sustained ventricular tachycardia for up to a week with the Novacor device in place, and it performed very well. Our last patient had ventricular fibrillation in the operating room before being placed on cardiopulmonary bypass for device removal and transplantation. Although pump flow was somewhat decreased, there was no appreciable drop in blood pressure. Pulmonary vascular resistance was less than 2 Wood units.

I was just wondering, Dr Cabrol, as the Jarvik heart is not available, how many times can you use the old ones?

DR CABROL: First I will answer an earlier question. One of the advantages of the artificial heart is not having to take care of fibrillation, tachycardia, or any kind of arrhythmia. Furthermore, it is a fantastic device in the way you can totally control the circulation. Of course, you still must have vasomotor tone. To answer your question,

we have always had enough devices for our use. Because we were using it regularly we have a lot of devices on our shelves. In addition we were able to obtain devices other teams did not want to use anymore. Perhaps Jack Cope-land can tell you about new developments with this device. There is some agreement with the University of Arizona, who will have the right to use the Symbion ventricular assist device and total artificial heart experimentally and clinically. If you need one of these devices, you can call us.

DR TIMOTHY B. ICENOGLE (Spokane, WA): One of the complications with implanting these devices is, of course, bleeding. And with transfusion of blood products comes the risk of exposure to other people's tissue antigens. Do any of the panelists have some suggestions on how to minimize that exposure when you are in one of these bleeding situations? They have resulted in some really disastrous situations with patients trapped on these devices with 100% positive PRAs.

MODERATOR PORTNER: It is certainly true that bleeding is the most common complication with all of these devices.

DR ICENOGLE: We have had no problems with high PRAs, although we have given patients tons of blood. Bleeding is a problem and we have lost patients a couple of days postoperatively because of transfusion of a large amount of blood products and right-sided resistance coming up. I think the most impressive recent experience was in a patient who had been on Inocor for a long time. The platelet count had dropped to about 16,000/ μ L and, in addition, they did not function. No matter how many times we took him back and how many attempts we made, the patient just bled to death. We could not control it. I would be very cautious of Inocor once it starts to affect platelet function.

DR JOHN C. NORMAN (Chicago, IL): I was only going to add to Dr Frazier's comment regarding the patient with a stone heart. It seems like it was a couple of weeks ago—actually, it was Valentine's Day 1978. We had an experience, in the experimental laboratory, of nearly 12 years implanting left ventricular assist devices without cardiopulmonary bypass. I remember our first publication regarding ventricular fibrillation with a left ventricular assist device in place—the animals were standing, with ventricular fibrillation. It was during that period in the laboratory that we examined the permutations of decreasing pulmonary vascular resistance. We found that all we had to do to get enough blood to pump was to increase the right-sided filling pressures to be on the right side of the Starling curve with the failing or fibrillating right ventricle. Ventricular fibrillation during left ventricular assist device implantation does not seem to be a big problem. You can manipulate the right heart. William Pierce had the same sort of experience in Hershey. Much of what has been presented regarding hemostasis has been worked out in clinical cardiac surgery.

MODERATOR PORTNER: Thank you, Dr Norman. Your timing as always is notable. Maintaining a normal systemic output without right ventricular function is essentially the basis of the Fontan procedure—low pulmonary vascular resistance. Any other comments? Questions?

SPEAKER: Have you ever seen a patent foramen ovale (PFO) cause problems with a Novacor? Has that been reported? To me it seems awfully hard to suck blood from the left ventricle. The only time I have gotten in trouble with a PFO was when I was draining the left atrium. But I guess it could.

DR FRAZIER: Patent foramen ovale has been reported as a problem when centrifugal and axial flow pumps are used, as you have just noted. That is the only instance where we have had that experience. I do not know, whether this has been reported with the Novacor.

MODERATOR PORTNER: There have actually been 3 patients with a PFO problem, but not recently. The large right to left gradient that is a result of elevated right atrial pressures and lowered left atrial pressure, secondary to left ventricular unloading, sometimes gives rise to a serious right to left shunt. Two of these patients were severely desaturated, requiring reoperation to close the PFO. The right atrium is now routinely explored for a PFO at the time of device implantation, and repaired as needed.

DR FRAZIER: If the mitral valve is functional, the left atrium will not experience excessive negative pressure. I place a single venous cannula, just as in any left-sided operation. We have a lot of trouble with bleeding in all these patients because of patient factors, as well as those associated with the pump. I know that in France, they have access to fibrin glue. Has that been of some benefit in treating these bleeding problems, Dr Cabrol?

PROF CABROL: But of course, the fibrin glue is very interesting—that is, to seal the suture lines. It is not easy to use on the total surface of a Dacron graft. But for the suture line it is very useful. I would also say that there is a big advantage in the internal ventricular assist devices because they take blood from the left ventricle. They also avoid any compression or problems with atrial cannulas, and this is very, very important. In that respect, the

implantable left ventricular assist device is almost like a total artificial heart on the left side because there is no real ventricular cavity. I think it is a very efficient quality of such device.

MODERATOR PORTNER: Thank you, Dr Cabrol. Doctor Loisançe?

DR DANIEL LOISANCE (Paris, France): Apparently, the bleeding is a real issue, and we are very fortunate in Europe because we can use aprotinin. The mechanism of action of aprotinin is extremely interesting. There are at least two mechanisms. One is the antifibrinolytic action. But the second, and much more important one, permits the normalization of platelet function. Platelets are activated by foreign surfaces and giving aprotinin at extremely high doses permits a return of the platelet function absolutely to normal. We have tried aprotinin in these patients and, just to give you an idea, a recent Novacor patient bled a total of only 150 mL. This has really changed the whole problem. The only thing we do not know for sure is the optimal dosage. We have been using the following protocol at the time of implantation: one million KIU during the operation and then one million KIU per hour for at least 12 hours. There is a lot to learn about aprotinin.

MODERATOR PORTNER: There certainly appears to be an advantage. It is not yet available in the United States, although I believe Dr Rose has used aprotinin in New York. Would you comment, Dr Rose?

DR ERIC A. ROSE (New York, NY): We have found that the way to get aprotinin is to start with another protocol, which for us was lung transplantation. Once you have some in your center it is usually possible to use it in other circumstances on a case by case basis and compassionate need. I will say this though, it is not a panacea. We have used it at the time of transplantation in explanting a device that had been in place for 324 days, I believe. It was a bloody operation despite the aprotinin; the patient required a lot of blood products.

I would also like to comment on the PFO issue. You can detect a PFO with transesophageal echocardiography. Just do a little bubble study before you get started. We have been doing that now too. If it is not there, then do not worry.

Nonpulsatile Circulatory Support: Techniques of Insertion

Moderator: George J. Magovern, Jr, MD

Panelists: Richard W. Wampler, MD, Lyle D. Joyce, MD, and Thomas H. Wareing, MD

MODERATOR MAGOVERN: We have this morning a learned panel to discuss the techniques of insertion of several assist pumps for postoperative circulatory support. The panelists include Dr Richard Wampler, Dr Lyle Joyce, Dr Thomas Wareing, and myself. Doctor Wampler will begin with a discussion of the Hemopump.

DR WAMPLER: Good afternoon, and thanks for your interest in this session. I want to spend some time today talking about some of the user-related issues of the Hemopump such as patient selection and insertion techniques. For those of you who are not familiar with the Hemopump, it is a high-speed turbine pump that spins at 25,000 revolutions per minute driven by an exotic speedometer cable. Blood is pulled from the left ventricle and is injected into the aorta. Soon to be introduced will be a pump that is for sternal or surgical insertion that injects blood into the ascending arch. One of the key features of this device is that it actively decompresses the ventricle as well as supporting the circulation. The Hemopump has a disposable element, pump assembly, and a console for electrical power and fluids that are needed to support the bearing mechanism of the pump. The console weighs about 11.25 kg; it provides all the information the motor needs to run and monitors system performance. An external drive motor is reusable and resterilizable.

Several versions of the Hemopump are in development or in some kind of clinical trial. The first device was intended for femoral insertion. It is about 23 cm in length and 8 mm in diameter. In addition, there is a sternotomy pump that is intended for surgical insertion. It was removed from the initial trials because of a problem with drive cable fracture but it is currently going to be reintroduced for clinical trials after some engineering breakthroughs that have allowed us to get much greater durability out of the drive cable and significantly greater flows from the pump. The sternotomy device has a much shorter cannula and is intended for insertion in the ascending arch. This device has flows of 5 L/min compared with the 3 to 3.5 L/min provided by the femoral device. The Hemopump generates peak velocities of 4 m/s, and we had a lot of concerns, originally, about hemolysis. However, this high-speed device is not a Waring blender for red blood cells, and red cell injury is on the order of one red cell for every 100,000 that pass through the pump.

I want to present a very brief summary of the clinical

results of a cardiogenic shock trial that was conducted in the United States and to briefly summarize the high points of this trial. We accepted 123 patients to the trial and were able to insert the device in about 80% of these patients. Regarding the mean hemodynamic values before insertion of the device for patients for whom we have preinsertion data, at $1.72 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ the patients met the criteria of less than $2 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$. The pulmonary artery wedge pressure was 26 mm Hg, well over the 18 mm Hg required, and the mean systolic pressure was 11 mm Hg less than the 90 mm Hg required.

Forty-two percent of these patients, for all diagnostic categories, survived to weaning and achieved ventricular recovery, and 27% were 30-day survivors. When this is broken down, although the numbers do not support statistical significance, I think there are some clear trends. Patients with acute myocardial infarction had very good left ventricular recovery (51.7%) and the best survival (34%). Patients who arrested after being weaned from bypass and in whom a catastrophic episode developed in the recovery room had the poorest survival, only 2 out of the total of 14 patients. Patients with cardiomyopathy, rejection of heart transplantation, had a fairly good survival at 30%.

Noninsertion was significantly greater in female patients than in male patients and has been a significant barrier to use. Noninsertion was primarily related to iliofemoral disease and an inability to get the pump up into the abdominal aorta. If it was possible to get the pump into the aorta the majority of patients underwent successful insertion, although in some patients it was difficult to get the cannula around the transverse arch because of a tendency of the cannula to go into the great vessels of the arch. Catheter guidance could be used for this but it is somewhat cumbersome and significantly prolonged the time of insertion. A rare patient could not be placed on support because it was impossible to pass the device past the aortic valve.

Loss of assistance did occur on some occasions and was predominantly due to the following causes: either the cannula was improperly placed or it migrated out of the ventricle. Drive cable fractures did occur and it was also possible, particularly in patients with acute myocardial infarction, for aspiration of preexisting mural thrombus and occlusion of the inflow of the pump to occur. Cannula ejection in the femoral device occurred 12 times in 11 patients. A contributing factor, we believe, in cannula ejection was the development of left ventricular recovery. Ejection generally occurred after patients began getting good contractility and pulsatility, and patients who had

cannula ejection had better survival than the overall group. Many of the patients with cannula ejection underwent removal of the pump without replacement because assistance was no longer needed.

Drive cable fracture is a sudden event that often occurs without warning. It is usually due to excessive bending of the drive cable. Drive cable fracture occurred in about 1 of 20 patients during the trial. It has been a big enough problem that we have redesigned the drive cable and believe that it will be a much less frequent problem in the future. A drive cable fracture will occur in an area of stress concentration that is very sensitive to small bend radii. Minimal stress can be achieved by providing a gentle curve of the drive cable and by attaching the motor to the patient so there is less possibility of kinking the drive cable when moving the patient.

Any device is vulnerable to user difficulties or problems in the field. One pump was returned to us from a patient who had serious hemolysis. On inspection, it was found that a Prolene suture was aspirated into the pump from the surgical anastomosis at the time of pump placement. A Hemopump is a very small-diameter pump so it will be sensitive to aspirate material, and this is something that needs to be very meticulously guarded against at the time of insertion. Also, preexisting mural thrombus can be aspirated into the pump, and that is a major issue in patients with acute myocardial infarction because 25% to 40% of such patients will have preexisting mural thrombus. In our experience, a mural thrombus was present 8 of 11 times in explanted pumps.

I want to spend a little time talking about the insertion of the sternotomy pump because it is the one that is going to be available in this country for clinical trials in 1992. The pump would be in the ascending arch, the tip in the midventricle away from the apex. This is a good device for surgeons because it does not require fluoroscopy for placement. We are recommending that a graft be anastomosed to the aorta for pump placement. The graft should be anastomosed to the outer curve of the ascending/transverse arch and exit the top of the sternotomy wound. Another technique is to tag the drive cable so that you can tell if the device has been inadvertently moved.

One of the difficult issues that we have wrestled, unsuccessfully, so far is proving clinical utility or measuring clinical benefit to the patient. This is necessary to get approval from the Food and Drug Administration (FDA), and this means that it has to be shown that there is benefit to the patient. Just improving cardiac index or improving blood pressure is not sufficient to demonstrate utility. It needs to be shown that patients have better survival, fewer complications, or shorter times in the intensive care unit. In addition, we also have to identify which patients are likely to benefit from the device. It is necessary to prove indications for use and predict what are the likely outcomes. We have done some statistical analysis correlating left ventricular power, although it is not a readily available number, with survival. The left ventricular power is calculated using mean blood pressure, pulmonary capillary wedge pressure and cardiac index, so it is difficult to have in the operating arena. The formula is left

ventricular work index = cardiac index $\times$ (mean arterial pressure - pulmonary capillary wedge pressure) $\times$ 13.6. The normal value is about 3,000. The Hemopump patients for the clinical trials had values less than 1,500. Patients who could not be weaned from assistance and patients who were weaned were separate statistically at a cutoff of approximately 1,000. Also, at the time of preinsertion for patients for whom we could calculate the value, there was a statistical difference between the work index at preinsertion between who could be weaned and those who could not. Survival was characterized by a very marked increase in ventricular power at 24 hours. In fact if a patient did not show a significant increase in ventricular power in 24 hours, the likelihood of survival was very low.

Our next strategy for the FDA is to look at patients at operation who have difficulty being weaned from the roller pump, and we will take these balloon pump candidates and randomize them against the Hemopump to evaluate survivability and potential patient benefit.

MODERATOR MAGOVERN: Experience with the Bio-Medicus pump at Allegheny General Hospital has been ongoing for more than a decade. The first insertion was performed in July 1980, in a 50-year-old woman after double coronary artery bypass grafting with normal left ventricular function who could not be weaned from cardiopulmonary bypass. Since that time, approximately 15,500 adult patients have undergone open heart operation at Allegheny General Hospital from July 1980 to July 1991, and 77 have required ventricular Biopump support.

The Biopump is a centrifugal pump composed of valveless rotator cones made from nonthrombogenic acrylics. These cones impart a circular motion to the blood, generating centrifugal force, pressure, and flow. The hydrodynamically designed flow path of the pump eliminates turbulence, cavitation, and resulting damage to the blood elements. A magnetic drive and a solid housing design prohibit air or contaminate induction.

The advantage of the pump in comparison with the external pulsatile pumps is that the Biopump is commercially available. It is not considered to be a true assist device by the FDA. As such, it has not been approved or disapproved as an assist device and is simply considered an extension of cardiopulmonary bypass. Needless to say, it is much less expensive than any of the federally approved devices.

As we will see, the Biopump provides temporary but adequate hemodynamic support with proper insertion techniques. The major disadvantage of the Biopump is that it is temporary, and cannulation techniques have necessitated that the patient remain bedridden. Ambulation is nearly impossible as the cannulas are secured with pursestring sutures and tourniquets. The cannulas are brought out through the sternotomy incision, making sternal closure difficult. As such, ambulation is impractical and hazardous as it might result in cannula displacement with resultant loss of flow.

Finally, the centrifugal pump provides for nonpulsatile flow. The external pulsatile pumps have been developed

with the assumption that pulsatile perfusion is critical for end-organ survival. It appears, however, that pulsatile flow may not be necessary for end-organ survival. The question remains unanswered. However, our clinical impression at Allegheny General Hospital is that end-organ survival is not dependent on pulsatile flow.

For left heart support, cannulation is achieved via the left atrium through either the left atrial appendage or right superior pulmonary vein, with return via a cannula in the aortic arch. The left atrial cannula is typically a 32F or 34F Sarns venous cannula. The Allegheny General Hospital group has exclusively used the right superior pulmonary vein for draining of the left ventricle. Other centers have described using the left atrial appendage or the roof of the left atrium. In our experience, these approaches are cumbersome and result in troublesome bleeding. The arch cannula is typically a 22F Bard right angle cannula that had been inserted for the open heart procedure.

For right heart support, the pulmonary artery is cannulated with a 22F Bard right angle cannula. It is the identical cannula used to cannulate the aorta. The right atrium is drained with the same cannula employed for the open heart procedure, typically a 51F two-stage Sarns cannula.

The equipment and supplies should include (1) the Bio-Medicus pump console, (2) Bio-Medicus disposable pump head, (3) Bio-Medicus flow transducer, (4) Bio-Medicus disposable flow probe, (5) sterile 3/8 inch $\times$ 3/16 inch tubing (approximately 10 feet), (6) tubing clamps (four), (7) priming solution (typically 3 L of Plasmalyte A), (8) a large sterile basin (5-L capacity), and (9) a battery pack. To initiate left ventricular assist and separate the patient from cardiopulmonary bypass, the following protocol is followed. Cardiopulmonary bypass flow is reduced gradually while the left atrial pressure is monitored by either a left atrial line or pulmonary artery wedge pressure. When the left atrial pressure reaches 20 mm Hg, assist flow is initiated. Cardiopulmonary bypass flow is then discontinued and the venous line is clamped. The aortic arch cannula is clamped, and the cardiopulmonary bypass perfusion line is quickly removed. The Biopump outlet line is then connected to the arch cannula. All air must be excluded from the connection and tubing at this time. Assist flow is initiated and increased incrementally. The total systemic blood flow (native ventricular output plus ventricular assist pump flow) is maintained at $2.2 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$. Left atrial pressure or pulmonary wedge pressure is maintained in the 5 to 15 mm Hg range by volume adjustment.

Most patients will have some degree of right heart failure when the left ventricular assist is initiated. If left ventricular assist pumping cannot maintain a $2.2 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ cardiac index with good cannula placement and adequate volume, then right heart failure is present and right heart assist may also be required.

Preparation and priming of the right-sided Biopump is completed as described for the left-sided Biopump. The right atrial cannula placed for cardiopulmonary bypass is connected to the inflow line of the second Biopump. The pulmonary artery catheter (typically, a 22F Bard right-

angle aortic arch cannula) is inserted into the pulmonary artery distal to the pulmonic valve and secured with pursestring sutures. Cannulas are brought out through the superior or inferior aspect of the incision. The skin is approximated, whereas the sternum is not. The perfusion lines are secured sutured to the skin and covered with several towels and a large adhesive plastic drape.

If the patient has no underlying rhythm or blood pressure with discontinuation of cardiopulmonary bypass, then one member of the surgical team will have to proceed with open cardiac massage while the other makes the necessary connections for biventricular assist. If the patient does have some ejection, however, open cardiac massage is not necessary and generally the patients have tolerated a brief period of hypotension without neurologic sequelae.

When a patient is on biventricular assist, coordination of the left and right flow rates requires manipulation of the pumps sequentially while closely monitoring the pulmonary artery pressure. The right assist pump flow is gradually increased while the left pump flow is incrementally raised to accommodate the right-sided output. The right assist pump must unload the right ventricle efficiently for the left assist pump to maintain a cardiac index of $2.2 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$. Left atrial pressure should be 5 to 15 mm Hg.

As mentioned previously, there have been 77 patients who have required assist pumping with the BioMedicus pump over the past decade. The vast majority of these patients have had the assist pumps inserted in the operating room. In the early days of the program, however, there were several patients placed on the assist device in the intensive care unit without the aid of cardiopulmonary bypass. Most of these patients had returned from the operating room with stable hemodynamics. Soon thereafter, however, the patient suffered an unheralded cardiac arrest requiring open cardiac massage in the intensive care unit. Cannulas for left and right heart assist were then placed in the intensive care unit. In reviewing this approach, the Allegheny General Hospital group would not recommend placing the cannulas in the intensive care unit without the aid of cardiopulmonary bypass. For people who arrest in the intensive care unit, our recommendation is to return the patient to the operating room as quickly as possible and place the patient on full cardiopulmonary bypass. Open cardiac massage can be performed during transport to the operating room. Placing the patient back on cardiopulmonary bypass ensures adequate perfusion to the brain. In reviewing the experience at Allegheny General Hospital with placing the cannulas in the intensive care unit, the incidence of neurologic injury was significantly greater. Thus, one could assume that placing the cannulas in the intensive care unit required prolonged episodes of hypotension resulting in neurologic injury. Once the patient is safely returned to cardiopulmonary bypass, then the purse-string sutures can be placed with meticulous attention, and the transfer to the Bio-Medicus pump can be done systematically and more safely. After cardiopulmonary bypass, heparin should be reversed with protamine.

After returning to the intensive care unit, the patient is not anticoagulated until clotting studies have normalized, after which administration of heparin is started to maintain activated clotting times greater than 150 seconds. The perfusionist on duty is responsible for performing activated clotting time monitoring and determining necessary heparin doses. Control of nonsurgical bleeding is accomplished by the administration of fresh frozen plasma, cryoprecipitate, and platelets to maintain coagulation profiles within normal limits. A disseminated intravascular coagulation profile should be obtained, and evidence of disseminated intravascular coagulation as determined by thrombocytopenia, hypofibrinogenemia, and increase in fibrin split products should be treated with appropriate blood products.

In the past, the centrifugal pump head was replaced every 48 hours. Over the past several years, the centrifugal pump has been allowed to function for 3 to 4 days with no abrupt failures. Thus, at this point, the pump head itself can be employed for at least 2 days and probably for 3 or 4 days.

Weaning of the assist pump is usually not attempted during the first 24 hours of assist support. Generally speaking, cardiac recovery requires at least 2 days. When the clinical picture is stable and cardiac recovery is suspected, weaning assessment can be completed. To assess left ventricular recovery, the Bio-Medicus pump flow rate is decreased to a rate that produces a rise in left atrial or pulmonary capillary wedge pressure to 20 mm Hg. At the same time, the arterial pressure waveform is monitored for signs of left ventricular ejection. For weaning the right ventricular assist pump, the right-sided pump flow is decreased while the right atrial pressure is monitored. Concomitantly, the pulmonary artery pressure wave form is monitored for evidence of right ventricular ejection. If after 1 minute of reduced flow no native ventricular ejection is apparent, the assist pump flow is returned to previous levels. If ventricular ejection is noted during weaning, a transesophageal echocardiogram is performed at the bedside. Staged weaning is guided by the degree of cardiac recovery as documented by cardiac output and transesophageal echocardiographic results. In addition, if ventricular ejection is noted during weaning, cardiac output can be calculated by both the thermodilution and Fick methods. If native ventricular output minus assist pump flow is greater than 2.2 L/min and all other patient parameters are stable, then the cannulas can be removed in the surgical intensive care unit or in the operating room under strict aseptic technique.

Generally the decision to remove the pumps is made in the operating room. Visual inspection of the heart is paramount with the aid of the Swan-Ganz catheter and the transesophageal echocardiogram. For removal of the pumps, 2,500 units of heparin is generally administered if bleeding has not been a major problem.

Before having Dr Lyle Joyce speak, I will ask the audience for questions for either Dr Wampler or myself. Before accepting questions, I would like to mention that Allegheny General Hospital has used on one occasion the Medtronic/Carmeda extracorporeal membrane oxygen-

ator system. It has just been delivered to Allegheny General Hospital within the past month. As you may know, the system essentially consists of a heparin-coated hollow fiber oxygenator, a disposable pump, sterile tubing, and various heparin-coated cannulas for the femoral artery or the aortic arch, and for the femoral vein or right atrium. In one of the more promising recent breakthroughs in the field of biocompatible materials, the Carmeda group has successfully developed a technique to bond heparin covalently to foreign surfaces. Our patient had undergone orthotopic cardiac transplantation and developed right heart failure after discontinuation of cardiopulmonary bypass. As such, the Medtronic/Carmeda extracorporeal membrane oxygenator system was used with a heparin-coated arch cannula and a heparin-coated two-stage right atrial venous cannula. The patient was maintained on full cardiopulmonary bypass without the use of heparin for 36 hours until another heart was secured. The circuit worked extremely well and there appeared to be minimal bleeding. In addition, the patient maintained excellent neurologic function as well as stable hepatic, pulmonary, and renal function. Thus, if faced with the choice between using the Medtronic/Carmeda system with two cannulas versus the biventricular Biopump system with four cannulas, I think at this point I would favor using the Medtronic/Carmeda system. Are there questions from the audience?

DR ROBERT P. McMANUS (Milwaukee, WI): We have also had experience with the Medtronic/Carmeda circuit and are pleased with it. The only caution I would make is that you have to make sure that your level of antithrombin III does not fall to less than 60% of normal. The antithrombin III level can fall to less than 60% of normal during long cardiopulmonary bypass times. Low antithrombin III levels may result in clotting of the Carmeda system. I have two questions. First, has aspiration of left ventricular thrombus by the Hemopump been a clinical problem? Second, has Allegheny General Hospital successfully exited the Biopump cannulas through the chest wall to close the sternum and allow the patient to possibly be weaned from the ventilator and ambulate?

DR WAMPLER: Aspiration of left ventricular thrombus has not resulted in neurologic injury but it has resulted in precipitous loss of pump flow in pump-dependent patients, resulting in two deaths.

MODERATOR MAGOVERN: The Allegheny General group has in a few patients instituted univentricular or biventricular support by exiting the cannulas through the chest wall and closing the sternum. In these cases the patients have generally not undergone open heart procedures but rather have been placed on a device for treatment of cardiogenic shock. In one instance, the patient was placed on the transplant list.

DR JOSEPH MOTAN (Providence, RI): At our hospital in Providence, Rhode Island, a second femoral artery type cannula is placed in the ascending aorta while the patient

is on cardiopulmonary bypass. Placing the second aortic arch cannula makes the transition to the ventricular assist device more efficient and prolonged episodes of internal cardiac massage are not required. For right ventricular assist pumping, the same cannula is placed through a pursestring suture in the right ventricular outflow tract and then passed through the pulmonic valve. Both of these cannulas are then tunneled underneath the sternum as one would do with a chest tube. The sternum is then closed, and our bleeding problems have been minimal.

MODERATOR MAGOVERN: That approach is attractive. There is no doubt that the aortic cannula is a troublesome site of bleeding. No matter how many pledgeted sutures one places circumferentially about the cannula, it generally bleeds.

SPEAKER: In our community hospital setting, we generally do not open the chest in the intensive care unit to initiate internal cardiac massage. Rather, our group has been able to place the patient on percutaneous bypass. Interestingly enough, when our group has placed a cannula through the infundibulum of the right ventricle and through the pulmonic valve, right-sided assistance has resulted in massive right ventricular distention secondary to pulmonic valve regurgitation.

DR ROBERT EVERETT (Minneapolis, MN): Our approach to placing the patients on the Bio-Medicus ventricular assist systems also uses transesophageal echocardiography. Our group attempts to differentiate between systolic dysfunction and diastolic dysfunction. If the patient has diastolic dysfunction, then our drainage cannula of choice is a metal-tipped right angle cannula placed in the left atrium through the right superior pulmonary vein. If the problem appears to be systolic dysfunction then we put the cannula across the mitral valve. In addition, the cannulas are then exited through separate stab wounds. The sternum is then closed in the standard fashion. This approach has been helpful in avoiding infectious complications and bleeding.

MODERATOR MAGOVERN: Is the metal-tip right-angle cannula an aortic arch cannula?

DR EVERETT: No, it is a 26F DLP right-angle cannula designed as a left ventricular vent catheter. The catheter is placed through the right superior pulmonary vein.

SPEAKER: Our group has used the Bio-Medicus centrifugal pump head for 6 or 7 days without changing the head.

MODERATOR MAGOVERN: Allegheny General has also used the pump head for 3 or 4 days. I do not think it is necessary to change the pump head every 2 days.

SPEAKER: Our group has transferred the patients to the intensive care unit on the operating room table. Soon

thereafter, decubitus ulcers have often developed in these patients. Has that also been the experience at Allegheny General Hospital?

MODERATOR MAGOVERN: Our experience has been very similar to yours. Presently the nurses place a specific decubitus pad soon after the patient's arrival in the intensive care unit.

DR VICTOR A. JEBARA (Paris, France): We have been using a technique designed at the Texas Heart Institute by Drs Duncan and Frazier. Briefly, a bifurcated coated Dacron graft is sewn to the ascending aorta. One limb of the graft is then used to pump blood into the aorta and the other limb is used to place a cannula through the aortic valve to the left ventricular cavity. In Paris, 5 patients have been treated with this technique, and transesophageal echocardiography has demonstrated minimal aortic insufficiency, no aortic stenosis, and excellent drainage of the left ventricle. The technique has also decreased bleeding at the cannulation site and has provided excellent left ventricular drainage. Doctor Magovern, do you have experience with this technique?

MODERATOR MAGOVERN: We have not had experience using Dr Frazer's technique. It is a novel idea. It certainly would allow you to close a chest and bring the graft through the chest wall.

DR ORDINON (Sweden): I have a question for Dr Wampler. If the Hemopump cannula migrates from the left ventricle into the ascending aorta, is it possible to steal blood from the coronary arteries or from the arch vessels?

DR WAMPLER: At present, this problem has not arisen. It is conceivable that if the cannula was near the coronary ostia, it might pull blood out from the coronary ostia. But so far no investigator has felt that this problem has occurred.

MODERATOR MAGOVERN: One last question.

DR RAUL GARCIA-RINALDI (San Turce, Puerto Rico): Doctor Magovern, do you find your patients on the Bio-Medicus pump accumulating a lot of free water, and how do you manage this problem? Do you specifically use a hemoconcentrator in your circuit?

MODERATOR MAGOVERN: Free water accumulation and subsequent total body edema is very common. The Bio-Medicus pump system is entirely preload-dependent. Thus, if there is ongoing bleeding or vasodilatation in the postoperative period, one must continue to give large amounts of volume.

DR JOYCE: At this time I will discuss only our experience with the Sarns and Bio-Medicus centrifugal pumps,

although we have used the Hemopump and are certainly excited about its future as well. Our experience began with the Centromed pump before Sarns purchased and sold it as the Sarns Delfin pump. Rather than giving a systematic description of our use of these devices, I will point out a few of the pitfalls that we have run into over the last several years, try to explain some of the changes that we have made in an attempt to overcome those problems, and then make a few comments about areas that we believe could use further improvements. We have found that if any system is going to work in the postcardiotomy cardiogenic shock setting, it has to be a system that can be very quickly and easily instituted. Invariably, one is at the end of a long case with multiple attempts having been made to wean from the heart/lung machine. At that point, no one on the team is in the mood for an ill-planned flailing attempt to try to get another system set up. Consequently, we have sterile packages at all times with the right lengths of tubing, the pump head, and all that is needed to quickly make a conversion once the decision is made that a ventricular assist device is needed. The perfusionist and the nurses set this up on the back tables while the surgeons are placing the pursestring sutures in preparation for inserting the cannulas. In the past, we had only straight cannulas to use for venous uptake. That created many frustrations in trying to figure out how to get the position just right so that the tubes would exit from the chest cavity in the appropriate direction to avoid any obstruction to the inflow to the pump. Fortunately, several companies have now manufactured angled cannulas with various rotations, such that practically any situation can be handled quite easily. I believe it is important to have a variety of cannulas available. When the decision to use a ventricular assist device is made, the perfusionists pull out an assortment of the cannulas available. We study the size of the heart and the configuration of the chest cavity and then select the one that we believe fits that particular patient best. The arterial cannulas are also now of multiple types. There are some acceptable ones, but I think there is room for improvement in this area. Longer cannulas are preferable in our experience because it is possible to exit them from the subcostal region such that the sternum can be closed more easily.

Initially, we brought all cannulas through the anterior chest wall. I have always believed in closing the sternum and, consequently, many times have needed to cut out a notch on each side of the sternum to bring the aortic cannula out directly through the sternum itself. We often either wire or suture the cannula directly to the bone. We now try to avoid this approach because it does limit the ability to move the patient freely in the postoperative period. With the newer cannulas, it is possible to bring all the cannulas out subcostally so that the sternum can be closed in a routine fashion. I also believe that it is important, if at all possible, to get the patient awake, extubated and moving in the early postoperative period. We certainly do not accomplish that in even a majority of the cases, but I believe that is something we should aim

for. I think with better cannulation techniques and anchoring procedures for these cannulas, it will be possible to do that rather routinely.

How do we prepare for cannulation? We do not prepare every surgical case for the potential need for a ventricular assist. However, we do routinely use a double pursestring suture of 3-0 Prolene in the aorta, and this is adequate to anchor the aortic cannula for initial hook-up of the left ventricular assist device. If a left ventricular vent is used, it is placed through the right superior pulmonary vein. A simple pursestring suture is used for the initial cardiopulmonary bypass run. If a ventricular assist device is needed, we then reinforce this line with a second and third row of sutures using pledgets all the way around such that we can buttress the tissue to the cannula. I agree with Jack Norman's comment this morning that any cannulation site needs to be buttressed with pledgets or some sort of a fringe on the tube that allows the tissue to be anchored directly to it. We have found the use of fibrin sealant very helpful. Many of you are involved in clinical trials for the Immuno Company, which is trying to get approval for the use of fibrin sealant in this country. Even if you do not have the luxury of having the Immuno fibrin sealant available, you can mix your own fibrin glue using equal parts of cryoprecipitate and thrombin. Gluing the sites of the cannulation may help in decreasing the amount of bleeding postoperatively.

The experience that we have had since May 1985 at the Minneapolis Heart Institute using these two pumps is a modest series of 57 patients. About half had left ventricular assist devices and went on to biventricular support. We have had patients supported from 1 to 16 days for an average of 4 days. Our average age is 55 years. The cannulation sites were as follows. In the left ventricular assist patients, the right superior pulmonary vein was thought to be the best spot for the left ventricular assist device uptake, although in some patients with large left atria, the dome of the left atrium between the aorta and the superior vena cava worked nicely. We used the ascending aorta in all patients for the inflow cannula. For right ventricular assist devices, all of our experience consisted of right atrium to pulmonary artery bypassing. Our results are similar to those of others. We have had about 35% of the patients die on the device, 65% were weaned, and 45% were ultimately discharged. There were some late deaths resulting in an overall present survival rate of 44%, with a majority of those patients being in New York Heart Association class I and II. We certainly believe that there is reason for optimism and reason to pursue efforts to make these techniques simpler and more efficient so that we can institute them at an earlier stage.

DR WAREING: I am an advocate of the centrifugal vortex system for several reasons. First, it is the only device available in most hospitals doing cardiac operations. The only devices are strictly investigational. Second, centrifugal pumps are the only devices that many surgeons are comfortable using.

However, as Dr Joyce and Dr Magovern mentioned,

better cannulas are needed. It is critical to close the chest after device insertion to decrease perioperative hemorrhage and infectious sequelae.

To help decrease postoperative bleeding, Dr Pennington's group uses fibrin glue. Thirty milliliters of cryoprecipitate is mixed with topical thrombin and calcium chloride and given in the two-syringe method.

The essence of the issue of pulsatile versus nonpulsatile flow remains problematic. To a certain extent, the issue cannot be easily answered because most patients with these devices are also supported by the balloon pump, which in essence provides pulsatile flow.

St. Louis University is also using transesophageal echocardiography. In the assist pump patients, it is indispensable. Our group is also involved with quantitating and semiquantitating a means to assess ventricular function on line with edge detection analysis and analysis acoustic back scatter. This system is several years from the clinical setting. To assess recovery of ventricular function clinically, our group decreases pump flow while giving an epinephrine challenge of 1 mL (diluted 1:10,000).

Interestingly enough, Dr Pennington does not believe advanced age (more than 65 years) should be a strict contraindication to assist device placement. We do not use age as a strict criterion for determining ventricular assist device insertion. Our results with patients older than 65 years are comparable with the results in patients less than 65 years of age.

The St. Louis group also supports using the vortex pump as the first line of support for postcardiotomy patients. If ventricular recovery is not dramatic and the patient is a potential transplant candidate, then a more permanent device can be inserted later. The centrifugal pumps are particularly useful in the first several days postcardiotomy. However, the incidence of neurologic and infectious complications rises rapidly after 1 week.

Finally, would Dr Magovern discuss in more detail the use of the centrifugal pump in managing patients with postinfarction ventricular septal defects?

MODERATOR MAGOVERN: In one instance, a patient with a postinfarction posterior ventricular septal defect in cardiogenic shock was treated with insertion of right- and left-sided Biopumps. The ventricular septal defect was not closed. Because the patient was in severe cardiogenic shock with a central venous pressure greater than 20 mm Hg, standard ventricular septal defect closure using cardiopulmonary bypass was considered hopeless as the mortality rate for this group of patients is in excess of 75%. The biventricular support was instituted to explore the possibility that his right ventricular function would significantly improve over 3 to 5 days. Over the course of 5 days, his right ventricle did dramatically recover. On the fifth day of support, the Biopump flow rates were decreased and the right and left ventricles both showed recovery. As such, the devices were removed. Unfortunately, however, the patient suffered a perioperative massive embolic stroke after removal of the devices. The cause of the embolic material was probably mural thrombus. It was a surprise to our group that the patient's right ventricular function would improve after such a massive myocardial infarction. Thus, in patients with a postinfarction ventricular septal defect, in cardiogenic shock, consideration should be given to placing the patients on ventricular assist devices as their myocardium may not be completely infarcted but may be ischemic or stunned. With 3 to 5 days of support, the ischemic or stunned myocardium may recover to the point that the patient could survive. In retrospect, however, it may have been more prudent to close the ventricular septal defect at the time of the device insertion.

SPEAKER: I enjoyed Dr Joyce's lecture and would like to ask him how he investigates for the presence of a patent foramen ovale at the time of device insertion.

DR JOYCE: Generally, our group has not opened the atrial septum to inspect for a patent foramen ovale at the time of device insertion.

Chronic Left Ventricular Support With a Vented Electric Assist Device

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Based on the success of the pneumatically powered HeartMate (Thermo Cardiosystems Inc, Woburn, MA) left ventricular assist device, researchers at the Texas Heart Institute have begun conducting clinical studies of the vented electric model in bridge-to-transplantation procedures. Like the pneumatic device, the electric device is implanted intraperitoneally, but the blood pump is powered through a percutaneous lead that is connected to two rechargeable batteries. The batteries are worn in a shoulder holster; thus, patients are not tethered to a

control console and are fully mobile. Two patients are currently undergoing left ventricular support with the vented electric HeartMate (duration of support, 315 days and 112 days) as they await cardiac transplantation, and they seem to be medically fit for outpatient care and follow-up. This technology may eventually allow selected patients to receive long-term support as a substitute for cardiac transplantation.

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The success of the pneumatically powered HeartMate (Thermo Cardiosystems Inc, Woburn, MA) left ventricular assist device (LVAD) has encouraged researchers in the field of mechanical circulatory support [1, 2]. This LVAD has been used in staged cardiac transplant operations, with the longest duration of support at the Texas Heart Institute being 233 days. We have found that patients are restored to better health as a result of improved circulation and, thus, end-organ function. Moreover, treatment with the HeartMate has been associated with a low risk of thromboembolic complications and infection. Currently, our research efforts are focused on the next generation of this technology, the vented electric HeartMate LVAD, which not only incorporates the best features of the pneumatic model, but also improves upon it by offering full patient mobility. This article will describe the vented electric LVAD and will provide a brief overview of our clinical experience.

Material and Methods

Description of Vented Electric Left Ventricular Assist Device

The HeartMate-1000 vented electric LVAD consists of an abdominally implanted blood pump and an external power source [1, 2]. The dual-chambered blood pump is housed within rigid titanium and measures 11.2 cm in diameter and 4.0 cm in thickness. The pumping chamber of the blood pump is capable of providing a maximum stroke volume of 83 mL, and the other chamber contains the electric motor. A polyurethane diaphragm that is bonded to a rigid pusher-plate separates the chambers. The inlet and outflow cannulas each contain a one-way,

porcine xenograft valve (Medtronic Blood Systems, Irvine, CA) to ensure unidirectional flow through the pump.

The vented electric LVAD receives power through a percutaneous lead, which is attached to a controller. The LVAD can be powered either by two lead-acid batteries, which are worn in a shoulder holster, or by a stationary control console. The control console can also recharge extra batteries.

The blood pump operates in either a fixed-rate or automatic mode. In the fixed-rate mode, the device pumps blood at a uniform rate and, thus, delivers a steady volume of flow. In the automatic mode, the pump ejects blood when the blood chamber is filled to 90% of its capacity, and, thus, the volume of flow varies in response to systemic circulatory requirements. The motor completes a single rotation for each pump ejection.

As in the pneumatic HeartMate, the electric LVAD features textured blood-contacting surfaces that promote formation of a stable biologic lining [3]. This lining has helped to reduce the risk of thromboembolic complications.

Implantation Technique

The vented electric LVAD is implanted in the same manner as the pneumatic LVAD, and the techniques have been described in detail [4, 5]. The operation begins with a median sternotomy incision, extending to above the umbilicus, after which cardiopulmonary bypass is instituted through standard techniques.

The left ventricular apex is cored with a special circular knife; then, the ventricular opening is reinforced with a sewing ring. The pump is placed intraperitoneally in the left upper quadrant, just below the diaphragm (Fig 1). An incision in the diaphragm allows the inlet cannula to be tunneled from the blood pump to the left ventricle. Pump outflow is achieved by anastomosing the distal end of a preclotted, woven Dacron graft to the ascending aorta,

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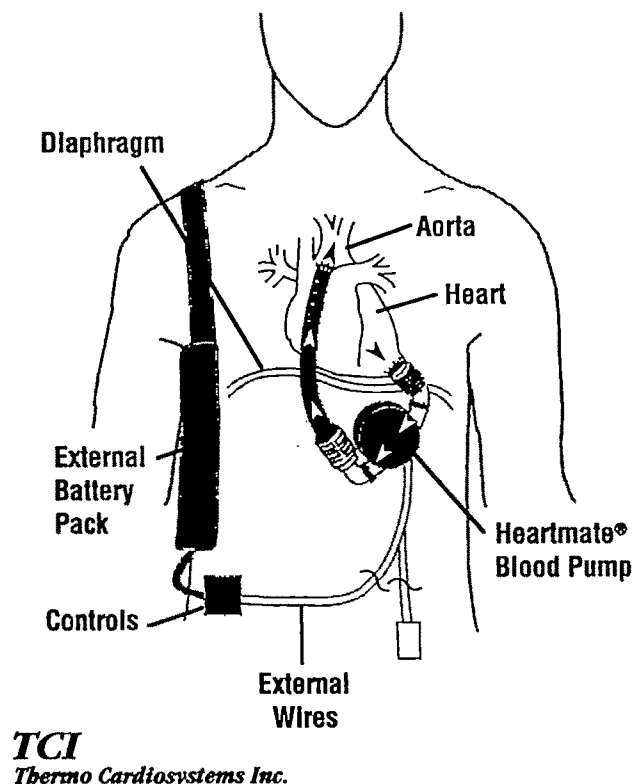


Fig 1. The vented electric HeartMate is implanted intraperitoneally. Power is provided through a percutaneous electrical lead. The rechargeable batteries are worn in a shoulder holster.

end-to-side, then connecting the proximal end to the pump. The electrical lead and vent tube are then tunneled percutaneously and exteriorized through the left lateral abdominal wall.

To begin left ventricular assistance, the pump is operated manually until air has been removed from the heart, the outflow graft, and the blood pump. Initially, the pump is set to operate at 50 beats/min; then, the rate is gradually increased, until an adequate volume is being delivered through the pump. Cardiopulmonary bypass flow is gradually reduced. Finally, a mediastinal tube and pleural tubes are inserted, and all incisions are closed.

Patient Management During Support

Experience obtained with the pneumatic HeartMate guides our current management of patients on the electric device. Once patients are hemodynamically stable, they are weaned from all vasoactive drugs and from mechanical ventilatory support. As soon as patients resume oral intake, they are placed on an antiplatelet regimen, consisting of aspirin (80 mg, once daily) and dipyridamole (75 mg, three times daily). Sodium warfarin is used if conventional indications, such as a pulmonary embolism, exist.

The major therapeutic goals include early mobilization of the patient, adequate nutritional support, and elimination of potential sources of infection. A physical therapist works with the patient as soon as possible to begin an

exercise program, often beginning in the intensive care unit. As the patient adjusts to the implantable blood pump, a registered dietician ensures that the patient's nutritional requirements are being met. To prevent infection at the site of the percutaneous lines, the area is cleaned three times daily with half-strength peroxide and saline solution and covered with a thin film of silver sulfadiazene. All intravenous lines and catheters are removed as soon as medically possible.

Evaluation of Pump Effectiveness

Pump parameters are adjusted to obtain physiologic flows of approximately 5 L/min. Hemodynamic data and laboratory values are monitored to verify efficacy of LVAD support. Serum creatinine and blood urea nitrogen levels are used to assess kidney function, and bilirubin levels are used to assess liver function. The pump's effect on blood components is monitored by measurement of hemoglobin level, plasma free hemoglobin level, and platelet count.

Study Criteria

In February 1991, the Food and Drug Administration granted the Texas Heart Institute approval to conduct five clinical implants with the vented electric HeartMate. As in the case of the pneumatic HeartMate device, only patients awaiting cardiac transplantation can be accepted into the study [1]. Patients are qualified to undergo staged transplant procedures with the HeartMate when their hemodynamic status continues to deteriorate, despite treatment with standard measures, including medical support, intraaortic balloon pump support, or both. The hemodynamic criteria for treatment include a pulmonary capillary wedge pressure of 20 mm Hg, with either a cardiac index of $2 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ or less or a systolic blood pressure less than or equal to 80 mm Hg.

The HeartMate cannot be used when a condition that would preclude cardiac transplantation is present. Exclusion criteria include severe pulmonary hypertension, severe renal dysfunction, and severe hepatic dysfunction. Finally, the size of the implantable pump precludes use in a person with a body surface area greater than 1.5 m^2 .

Results

Between May 1991 and April 1992, 4 patients with idiopathic cardiomyopathy underwent implantation of a vented electric HeartMate LVAD. Their average age at the time of implantation was 47 years, and the average body surface area was 2.16 m^2 (range, 2.09 m^2 to 2.26 m^2).

Treatment is on-going in the second and fourth patients in this series. Patient 2, a 33-year-old man, has been supported for 315 days, and patient 4, a 49-year-old man, for 112 days. Kidney and liver dysfunction in these patients have been reversed, as assessed by comparing laboratory values obtained before and after implantation (Table 1). Each patient's overall medical condition has also improved, as evidenced by an upgrade in New York Heart Association functional class status from class IV before implantation to class I after implantation.

The first patient, a 52-year-old man, was supported for

Table 1. Improvement in Kidney and Liver Function in Patients Receiving Continuing Treatment

Variable	Patient 2		Patient 4	
	Before	3 months	Before	3 months
Kidney function*				
Serum creatinine (mg/dL)	0.9	0.9	4.2	1.5
Blood urea nitrogen (mg/dL)	15	11	43	10
Liver function*				
Total bilirubin (mg/dL)	4.2	0.5	1.8	0.7

* Laboratory values shown were obtained before left ventricular assist device treatment and 3 months after left ventricular assist device treatment was initiated.

14 days, with the average pump index being greater than $2 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$; however, he had irreversible end-organ dysfunction related to massive operative and peri-operative hemorrhage (>100 units), which resulted in death. The third patient, a 54-year-old man, died intraoperatively of hemorrhage.

Comment

Two of our patients continue to receive left ventricular support with the vented electric HeartMate because of the inability to locate suitable donor hearts for cardiac transplantation. Despite the long duration of support in patient 2, he is in good health and has not experienced adverse consequences. Both patients seem medically fit for outpatient care and follow-up.

Based on our more extensive study of the pneumatic LVAD and on our early experience with the electric LVAD [1, 2], the potential for providing long-term left ventricular support has greatly improved. The outcome of patients undergoing treatment with the pneumatic HeartMate before transplantation compares favorably with that of our historical transplant patients [6]. Despite progress in

the field of cardiac transplantation, the donor heart shortage continues, and posttransplantation complications, such as accelerated coronary atherosclerosis, limit the potential for a satisfactory long-term outcome. Thus, we need to explore alternatives to cardiac transplantation.

For some patients with chronic left ventricular failure, the alternative to cardiac transplantation may be a permanently implantable LVAD. Whereas patients receiving HeartMate treatment as a bridge to transplantation have enjoyed better health, the quality of their lives is expected to improve even further with the electric system, which allows them to move about freely, untethered to control consoles. Ultimately, we hope to discharge LVAD patients from the hospital, allowing them to return to their normal activities at home and at work. This technology may, in selected patients, be adequate for long-term support as an eventual substitute for cardiac transplantation.

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Univentricular and Biventricular Thoratec VAD Support as a Bridge to Transplantation

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As of October 1991, the Thoratec ventricular assist device (VAD) system has been used in 154 transplant candidates who were in imminent risk of dying before donor heart procurement at 39 medical centers in 10 countries. The VAD system consists of a prosthetic ventricle with a 65-mL pumping chamber made from Thoratec's BPS-215M polyurethane, cannulas for atrial or ventricular inflow and arterial outflow connections, and a pneumatic drive console. The devices can be used for partial or complete support of the pulmonary, systemic, or both circulations. In all patients (average age, 42 years; range, 11 to 64 years), the pumps were placed in a paracorporeal position on the anterior abdominal wall and connected to the heart and great vessels by cannulas crossing the chest wall. Biventricular support was used in 120 patients (78%) and isolated left VADs were used in 34. Average

flow rate was 5.0 ± 0.9 L/min for the left VAD and 4.3 ± 0.8 L/min for the right VAD. The most frequent complications were bleeding (42% incidence, 7% mortality) and infection (36% incidence, 8% mortality). Ninety-eight patients (65%) recovered sufficiently to undergo heart transplantation after 8 hours to 226 days of support (average, 17.5 days), and 3 are waiting on VADs for transplantation. Eighty-two patients who received transplants have been discharged. This is an 84% early post-transplantation survival and a 54% overall survival. The actuarial survival 1 year after transplantation is 82%, comparable with that of conventional heart transplantation. We conclude that these heterotopic prosthetic devices provide an effective method of maintaining blood flow to vital organs until a donor heart can be procured.

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The use of unilateral or bilateral prosthetic ventricles and artificial hearts in patients who are in imminent risk of dying before a donor heart becomes available has become a standard method of supporting the circulation before heart transplantation [1, 2]. Bridging to transplantation is a two-step process requiring implantation of the support device and subsequent orthotopic cardiac transplantation. The Thoratec ventricular assist device (VAD) system was first used successfully as a bridge to transplantation in September 1984. We previously presented reviews of the results with this device in the first 29 patients [3] and 72 patients [4]. The following is an updated report of the current experience in 154 patients as of October 1991 who had circulatory support with Thoratec VADs for left-sided support only or for left plus right support as a bridge to heart transplantation. Results from patients with mixed types of support systems, such as Thoratec VADs used in combination with centrifugal pumps, are not included.

Material and Methods

The studies in the United States were conducted under investigational device exemption regulations, with protocol and patient consent forms approved by the institu-

tional review boards and by the United States Food and Drug Administration. Informed consent was obtained from either the patient or next of kin.

Ventricular Assist Device

The Thoratec VAD system consists of prosthetic ventricles with a 65-mL stroke volume, appropriate cannulas for atrial or ventricular inflow and arterial outflow connections, and a pneumatic drive console (Figs 1, 2). The blood pumping chamber and cannulas are fabricated from Thoratec's BPS-215M polyurethane elastomer, a blend of two polymers, one of which provides extensive flex life and strength; the other provides thromboresistance [5]. The pneumatic drive console (see Fig 2) provides alternating positive and negative air pressure to empty and fill the blood pump and has three control modes depending on the needs of the patient: asynchronous (fixed rate), volume (full-to-empty variable rate), and synchronous [6]. The full-to-empty mode was used in most bridge cases, because it automatically adjusts beat rate and thus flow output in accordance with venous return and the needs of the body. These heterotopic prosthetic ventricles are placed in a paracorporeal position on the anterior abdominal wall and are connected to the heart and great vessels with cannulas crossing the chest wall (Fig 3). For support of the left side of the heart, inflow cannulation can be achieved from the left atrial appendage, from the left atrium through the interatrial groove, or from the left ventricular apex, depending on the patient's anatomy or the surgeon's preference. Ventricular assist device outflow is through a polyurethane cannula attached to a preclotted 14-mm polyester graft anastomosed to the

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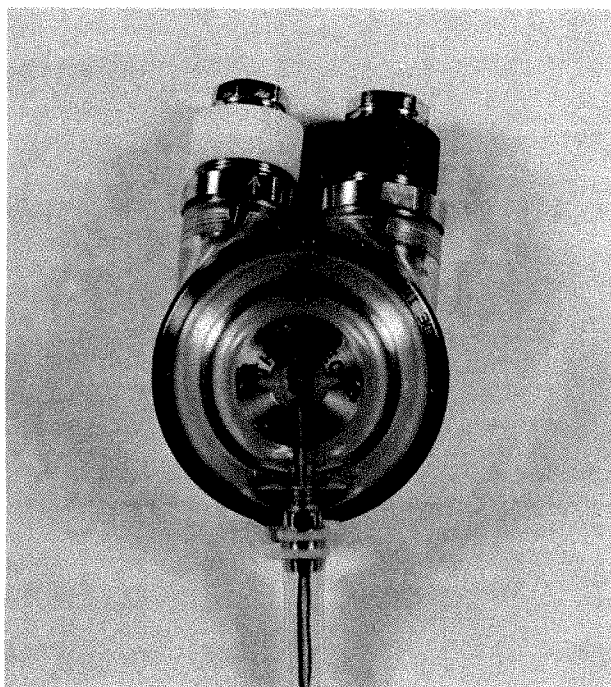


Fig 1. The Thoratec ventricular assist device has a flexible polyurethane blood pumping chamber in a rigid plastic housing. The effective stroke volume is 65 mL.

ascending aorta. For support of the right side, cannulation is from the right atrium with return blood flow to the pulmonary artery. Detailed surgical techniques for these cannulation approaches have been previously published [7].

Patient Population

One hundred fifty-four patients awaiting heart transplantation who were in imminent risk of dying before donor heart procurement received Thoratec VADs for left or biventricular support at 39 medical centers in 10 countries. Coronary artery disease (either ischemic cardiomyopathy or acute myocardial infarction) had been diagnosed in 65 patients (end-stage ischemic heart disease in 43 patients and acute myocardial infarction in 22), cardiomyopathy in 73 patients (hypertrophic in 2, known viral in 7, postpartum in 9, and idiopathic in 55), and graft failure after prior orthotopic cardiac transplantation in 8 patients (early failure in 3, late failure in 5). An additional 8 "other" patients received devices (3 with valvular disease, 3 with myocarditis, 1 with doxorubicin hydrochloride toxicity, and 1 with transposition of the great vessels). There were 121 male and 33 female patients with an average age of 42 years (range, 11 to 64 years), an average body surface area of 1.84 m^2 (range, 1.06 to 2.41 m^2) and an average weight of 73 kg (range, 30 to 123 kg).

Preoperative Status

Before the implantation procedure, all patients were receiving maximal inotropic support, 64 (42%) had one or more cardiac arrests, 99 (64%) received cardiac assistance

with intraaortic balloon pumps, and 89 (58%) were receiving mechanical ventilation. Despite this therapy, the average cardiac index was $1.4 \pm 0.9 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ with a pulmonary capillary wedge pressure of $30 \pm 8 \text{ mm Hg}$. The decision to implant VADs was made when the clinical and hemodynamic status indicated that the patient would probably die before a donor heart could be located.

Results

As of this writing, 3 of the 154 patients remain on Thoratec VADs for circulatory support while a suitable donor becomes available. Results are therefore reported on 151 patients.

Hemodynamics

Blood flow from the VADs maintained the circulation for up to 226 days until a donor heart could be located and heart transplantation performed. Blood flow from the left VADs averaged $5.0 \pm 0.9 \text{ L/min}$ (flow index, $2.7 \pm 0.5 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$), whereas flow from the right VADs averaged $4.3 \pm 0.8 \text{ L/min}$ (flow index, $2.3 \pm 0.4 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$) (Fig 4).

Of the 151 patients who received VADs with the intention of bridging to transplantation, 98 (65%) recovered

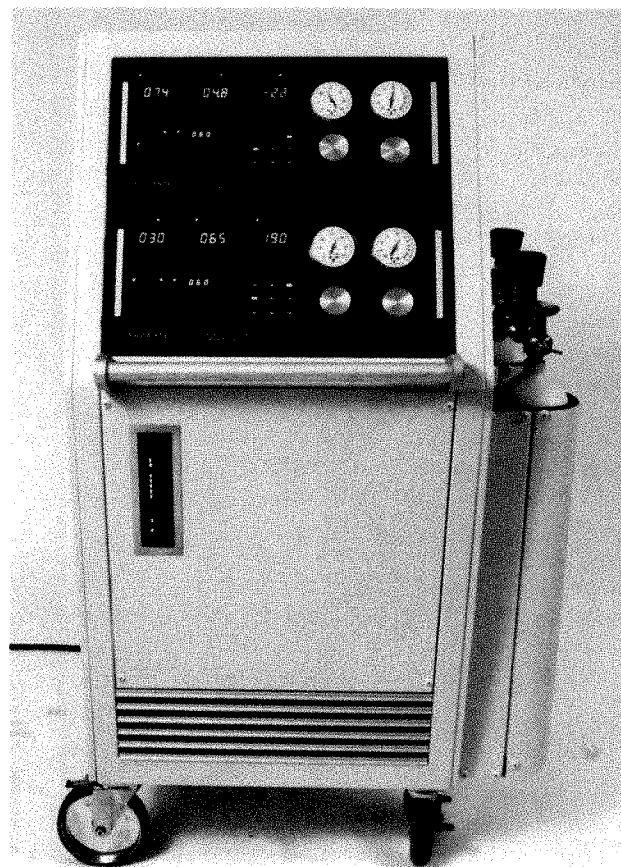


Fig 2. The Thoratec ventricular assist device drive console has two independent pneumatic drive modules for univentricular or biventricular support.

sufficiently to receive heart transplants, and 82 of those were discharged from the hospital (Table 1). Thus the early posttransplantation survival was 84% and the overall survival from implantation to patient discharge was 54%. Most (78%) received biventricular support. In 34 patients (22%) univentricular left VADs were sufficient to support the circulation. The survival statistics for the 32 patients with univentricular left VADs (87% after transplantation, 63% overall) were not significantly different than for the 119 patients with biventricular support (83% after transplantation, 52% overall).

Age

The survival statistics divided into three groups according to age are shown in Table 2 (data for 137 patients). Although the overall survival from VAD implantation to patient discharge showed a slight decrease with age (63%

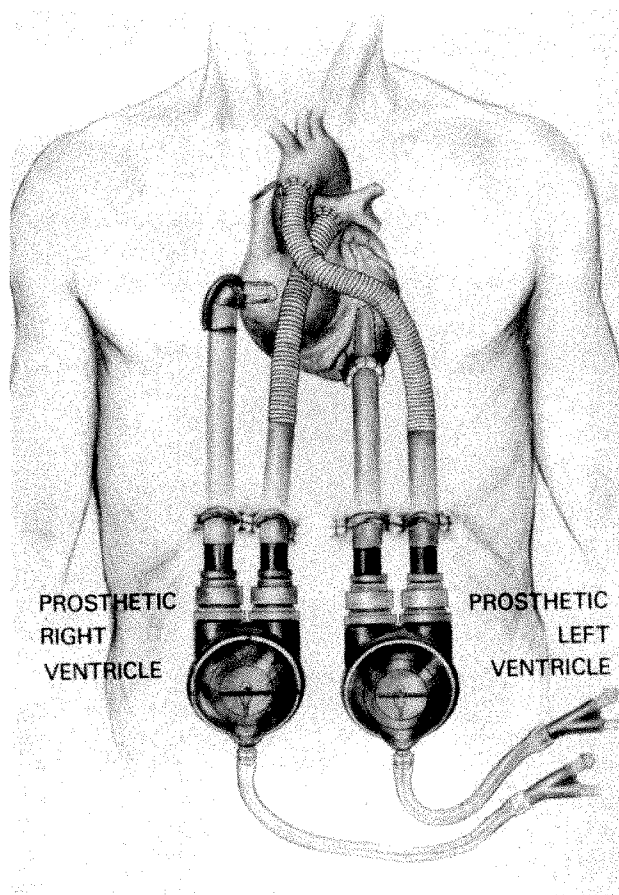


Fig 3. An example of biventricular support is shown with two ventricular assist devices in a paracorporeal position, functioning as right and left prosthetic ventricles. Left ventricular apex cannulation is illustrated in this example, although left atrial cannulation can also be used. Isolated left heart support can be achieved with a single ventricular assist device. (Reprinted from Hill JD, Farrar DJ, Hershon JJ, et al. Bridge to cardiac transplantation: successful use of prosthetic biventricular support in a patient awaiting a donor heart. *Trans Am Soc Artif Intern Organs* 1986;32:233-7, by permission.)

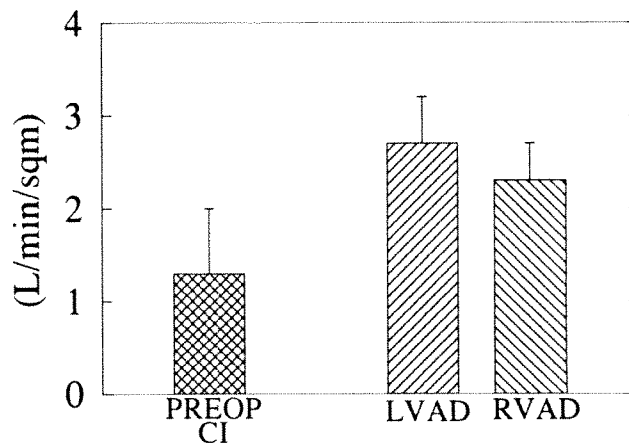


Fig 4. The average ventricular assist device blood flow index during bridging to transplantation is significantly greater than preoperative cardiac index (CI). In addition, left ventricular assist device (LVAD) flow is slightly greater than right ventricular assist device (RVAD) flow.

in patients less than 40 years, 53% in patients in their 40s, and 49% for patients 50 and over), posttransplantation survival for patients 50 and over (83%) was actually better than for patients in their 40s (76%) but not as good as for those patients less than 40 (91%).

Duration of Ventricular Assist Device Support

The median duration of all bridge cases was 7 days (mean, 17 days), and the range was from 1 hour to 226 days. Of note, in the past 12 months the median duration of support increased to 12 days (mean, 23 days). Survival by duration of support is seen in Table 2 (data for 137 patients). There were 69 patients who had VADs for less than 7 days, 43 patients for 7 to 30 days, and 25 patients from 30 to 226 days. The percentage of patients who underwent transplantation was not significantly different (65% to 68%) between the three groups. The posttransplantation survival for those supported less than 7 days (89%) appeared to be greater than that for those supported for 7 to 30 days (79%) or more than 30 days (76%), but that did not reach statistical significance. The overall survival was similar for the three groups (58% to 52%).

Diagnosis

Sixty-three patients (42%) had coronary artery disease diagnosed, and 73 patients (48%) had nonischemic cardiomyopathy (Table 3). The results are almost identical for these two groups. Within the cardiomyopathy group, the patients with diagnosed viral cardiomyopathy did especially well, although the numbers of patients in the nonidiopathic subgroups are too small to draw any conclusions. Within the coronary artery disease group, the 22 patients with acute myocardial infarction had a better survival rate (100% posttransplantation survival) than the 41 with chronic end-stage ischemic disease (70% posttransplantation survival).

Table 1. Overall Survival Statistics for Patients Who Received Thoratec Left or Biventricular Assist Devices as a Bridge to Heart Transplantation^a

Support	Implanted (No.)	Transplanted		Survival		
		No.	Percent	No.	After Tx (%)	After Implantation (%)
LVAD	32	23	72	20	87	63
BVAD	119	75	63	62	83	52
Total	151	98	65	82	84	54

^a Does not include data on 3 patients waiting for a transplant at the time of this report.

BVAD = biventricular assist devices; LVAD = left ventricular assist device; Tx = transplantation.

Complications

Complete data on complications are available for 137 patients who received Thoratec VADs for bridging to transplantation (Table 4). Bleeding, the most common complication during the bridge period, was reported in 58 patients (42%). Reoperation to control bleeding was required in 32 patients, and bleeding was reported as the cause of death (Table 5) in 10 patients (7%). Infection was another major complication, occurring in 49 patients (36%) and causing death in 11 patients (8%). Renal failure was reported in 50 patients (36%), 24 of whom required dialysis during the bridge period. Fifteen patients succumbed to multiorgan failure, which was the most common cause of death in patients who did not survive to transplantation. Hepatic failure was reported in 24% of patients. Hemolysis (defined as a plasma free hemoglobin measurement greater than 40 mg/dL) was seen in 26 patients (19%) on the device, usually only transiently in the first week or two. However, only 3 patients required transfusion. Respiratory failure occurred in 24 patients. Nonthromboembolic neurologic events were reported in 19 patients, including 4 patients who died before transplantation of brain death believed in retrospect to be present before VAD insertion. Embolic events occurred in 11 patients (8%), 8 of whom also had infection complications at the same time. Two patients died before trans-

plantation after cerebrovascular accidents. One patient with a unilateral left VAD died before transplantation with right ventricular failure, and 1 patient died when adequate inflow through the left VAD cannula could not be achieved.

Seven patients who underwent transplantation died of graft failure before discharge. Additional deaths reported after transplantation but before discharge from the hospital were caused by infection in 4 patients, bleeding in 3 patients, and rejection in 1 patient.

Actuarial Survival

The actuarial survival for those who underwent transplantation is shown in Figure 5, along with the survival for conventional heart transplantation according to the Registry of the International Society for Heart and Lung Transplantation [8]. The 1-year survival rate for the patients bridged to transplantation with the Thoratec VAD was 82%, compared with 81% for conventional transplantation as reported in the registry.

Comment

Since our last multicenter report [4], the number of bridge to transplantation procedures with the Thoratec VAD has more than doubled from 72 to 154. Approximately two-

Table 2. Survival Statistics by Patient Age and Duration of Support for Patients Who Received Thoratec VADs as a Bridge to Heart Transplantation (n = 137)

Variable	Implanted (No.)	Transplanted		Survival		
		No.	Percent	No.	After Tx (%)	After Implantation (%)
Age (y)						
<40	49	34	69	31	91	63
40-49	47	33	70	25	76	53
>50	41	24	59	20	83	49
Duration (days)						
<7	69	45	65	40	89	58
7-30	43	29	67	23	79	53
>30	25	17	68	13	76	52

Tx = transplantation; VAD = ventricular assist devices.

Table 3. Comparison of Survival by Diagnoses of Coronary Artery Disease and Cardiomyopathy

Diagnosis	Implanted (No.)	Transplanted		Survival		
		No.	Percent	No.	After Tx (%)	After Implantation (%)
Coronary artery disease						
Acute myocardial infarction	22	15	68	15	100	68
End-stage ischemic disease	41	27	66	19	70	46
Subtotal	63	42	67	34	81	54
Cardiomyopathy						
Idiopathic	55	35	64	30	86	55
Viral	7	7	100	5	71	71
Postpartum	9	6	67	5	83	56
Hypertropic	2	1	50	1	100	50
Subtotal	73	49	67	41	84	56

thirds of patients implanted have survived to receive a heart transplant (down slightly from three-fourths), whereas the posttransplantation survival through hospital discharge stayed relatively constant (from 83% to 84%) and is comparable with routine heart transplantation without VAD support. The results again emphasize the importance of patient selection and early implantation as the principal factors influencing survival. Patients who died of multiorgan failure and pre-VAD neurologic hypoxia are examples of patients in whom restoration of blood flow with VAD support was too late to reverse preexisting conditions. Unfortunately, it is often clear only in retrospect that the window of opportunity was missed, and making the decision to proceed with early intervention continues to be a challenge. There is continued debate over the best indications for use. The ideal candidate is in imminent risk of dying of irreversible myocardial damage but without end-organ involvement or contraindications to heart transplantation. The hemo-

dynamic guidelines used in the clinical investigation (cardiac index less than $1.8 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ and pulmonary capillary wedge pressure greater than 20 mm Hg) have been useful for study purposes but sometimes are inappropriate indicators in patients who are clinically deteriorating before satisfying these criteria.

Most surgical teams continue to prefer biventricular devices, which comprised 78% of the implants. As Pennington and associates [9] have reported, there does not appear to be any difference in morbidity or mortality in using biventricular or univentricular devices. Many patients, of course, do very well with isolated left VAD support, as illustrated by the patient with the longest left

Table 4. Complications Reported in 137 Patients While on Thoratec VADs for Bridging to Transplantation

Complication	No.	Percent
Bleeding (reoperations: 32)	58	42
Renal failure (dialysis: 24)	50	36
Infection	49	36
Hepatic failure	33	24
Hemolysis	26	19
Respiratory failure	24	17
Multiorgan failure	22	16
Non-TE neurologic events	19	14
Emboli (including 8 septic)	11	8

TE = thromboembolic; VADs = ventricular assist devices.

Table 5. Causes of Death (before hospital discharge) Reported in 137 Patients Bridged to Transplantation

Cause of Death	No.	Percent
Patients not transplanted (46/137)		
Multiorgan failure	15	11
Sepsis	11	8
Bleeding	10	7
Brain death (preexisting)	4	3
Respiratory failure	2	1.5
Stroke	2	1.5
RV failure	1	0.7
Inadequate LVAD filling	1	0.7
Total	46	34
Transplanted patients (15/91)		
Graft failure	7	8
Infection	4	4
Bleeding	3	3
Rejection	1	1
Total	15	16

LVAD = left ventricular assist device; RV = right ventricular.

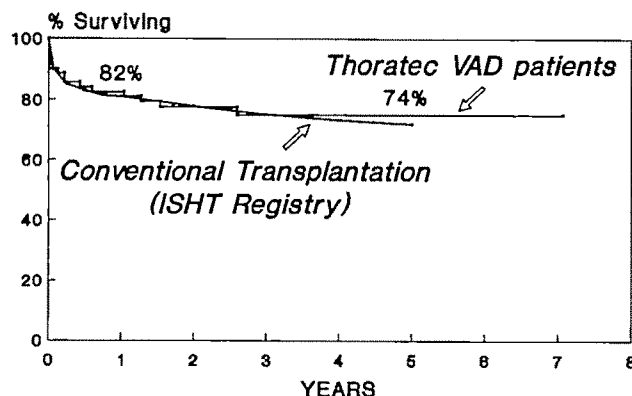


Fig 5. The actuarial posttransplantation survival of Thoratec ventricular assist device (VAD) patients (82% at 1 year and 74% at 5 years) is comparable with that of conventional heart transplantation. (ISHT = International Society for Heart and Lung Transplantation.)

VAD support period in this series of 226 days, who underwent successful transplantation and was discharged alive. However, early implantation appears to be especially important for successful univentricular support, because of potential worsening right heart function or increasing pulmonary vascular resistance. Unfortunately, there are no clear-cut predictive guidelines from this study or from other devices on how to decide whether one or two VADs should be used. Often the right VAD is implanted from the onset to assure against potential right ventricular failure, as the risks of the right VAD are considered small compared with potential risks of right heart failure or a reoperation to implant a right VAD at a later time. Biventricular devices are especially indicated in patients with severe, potentially lethal arrhythmias, and they have successfully supported patients with prolonged ventricular fibrillation or asystole.

The principal advantage of the Thoratec VAD System is its versatility. It can be used for univentricular or biventricular support, left heart cannulation can be accomplished through the left atrium or the left ventricular apex, and the paracorporeal approach allows it to be used in a wide range of patient body sizes, the smallest of which in this series was a body surface area of 1.06 m² in an 11-year-old patient. The device can also be used for support pending recovery of the natural heart [10, 11], as well as for bridging to transplantation.

The preferred cannulation method for bridging to transplantation is the left ventricular apex. A greater flow rate can be achieved (5.5 to 6.5 L/min) compared with left atrial cannulation (4.0 to 4.5 L/min), and there is decreased risk of stasis-induced mural thrombus occurring because blood flow continues through the left ventricular chamber and out the apex. However, if cardiac recovery is a possibility, then atrial cannulation, through either the base of the left atrial appendage or the interatrial groove, is the preferred method to avoid damage to the left ventricle during apex cannulation. Atrial cannulation was recently used in a 19-year-old patient with profound heart failure from acute myocarditis, where the original intent

of bridging the patient to transplantation was changed when his cardiac function showed improvement [11]. The patient was weaned from the left VAD after 70 days and was discharged alive with normal cardiac function.

The median duration of VAD support in 1990 and 1991 has increased to 12 days from 4.4 days as we reported before 1990 [4]. The number of patients supported for longer than 30 days also has increased from 14 to 25, and the longest duration increased from 81 to 226 days. Durations of VAD support are directly related to the time required to find a donor heart, which varies considerably, with some centers always finding hearts in a week or two, and others routinely requiring several months.

Because of the uncertainty of the support duration and the realization that infection is one of the major late complications, patient management should emphasize infection control from the onset. There does not appear to be any pattern to the sites or organisms involved, and device-related infections generally are not a major problem. These are usually limited to superficial percutaneous cannulation sites without involvement into the chest even in the longest cases. All attempts should be made to stop bleeding in the initial implant procedure. Not only is bleeding (surgical and coagulopathy related) a major complication in itself, as noted by Gray and associates [12], but reoperations to control bleeding also increase the risk of late infection. Monitoring lines should be pulled and the patient should be extubated as soon as possible, and ambulation and exercise is encouraged [13].

It should be emphasized that preparation and team training are absolutely mandatory for any successful circulatory support program with the Thoratec VAD or any other device. The roles of hospital support staff should be clearly identified and the team organized and trained [14]. Nursing protocols should be set up [15] and continuing education provided to meet the needs of circulatory support patients.

In conclusion, the Thoratec VAD system provides a versatile means of univentricular or biventricular circulatory support as a bridge to cardiac transplantation in critically ill patients, with posttransplantation survival rates comparable with that of conventional heart transplantation.

We gratefully acknowledge the contributions of the numerous investigators and circulatory support teams at the 39 hospitals who participated in this ongoing study.

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Use of the Symbion Biventricular Assist Device in Bridging to Transplantation

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From 1988 to 1991 13 patients received Symbion biventricular assist devices in attempts to bridge them to cardiac transplantation. All 7 of those who had cardiac transplants survived to hospital discharge. One death occurred 60 days after transplantation because of rejection. All other patients who received transplants are surviving. Implant times in this group varied from 10 to 164 days (mean, 55 days). There were two embolic neurologic events and two significant infections, and 2 of the survivors were dialyzed for reversible renal failure

before transplantation. Of those who died on device support, 3 presented on centrifugal pump support. The three other deaths were caused by graft rejection, multiple organ failure, and multiple peripheral emboli. Biventricular assist devices optimally provide cardiac outputs of 4 to 5 L/min, can be quickly inserted often without requiring cardiopulmonary bypass, are easily explanted, and seem best suited for patients weighing less than 80 kg.

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Since the first bridge to transplantation experiences [1-3], devices of various types have been used for days to months to support the circulation. The orthotopic pneumatic biventricular device experience has essentially been confined to the Symbion total artificial heart [4, 5]. The heterotopic, paracorporeal pneumatic biventricular support experience has been largely with the Thoratec device (Berkeley, CA) [3, 6], and the left ventricular heterotopic electromechanical experience has been primarily with the Novacor device (Oakland, CA) [2, 7]. Each of these devices as well as several others [8, 9] have been successful in bridging to transplantation, and although none has enjoyed outstanding success with heart recovery after cardiac operation, the univentricular and biventricular paracorporeal devices have had the best record [10, 11].

Our experience with the total artificial heart is reported elsewhere [4], but our favorable experience with the Symbion ventricular assist device in a biventricular configuration has not previously been reported.

Material and Methods

The Symbion acute ventricular assist device is a pneumatically driven, paracorporeal, pulsatile ventricular assist device. This device may be used for left, right, or biventricular support. Since April 1988 we have used the Symbion acute ventricular assist device exclusively as a biventricular device.

The device was used in 13 patients who remained in

cardiogenic shock despite adequate filling pressure, optimal inotropic support, and when appropriate, intraaortic balloon pump counterpulsation. Three patients were transferred from outside institutions on centrifugal assist (2 in a biventricular configuration, 1 with a left ventricular assist device) with intraaortic balloon pump counterpulsation. Some patients were electively placed on the Symbion while awaiting transplantation. Others were placed emergently before or during a transplant evaluation. The devices were used as an extension of other physiological support measures, such as inotropes and intraaortic balloon pumping. Drive mode was asynchronous so as to allow optimal filling of the prosthetic ventricles and thus maximize cardiac output.

Implantation was accomplished without the use of cardiopulmonary bypass in 3 of the 13 patients (patients 8, 9, and 13). For left heart support, inflow is accomplished by insertion of a right-angle 51F cannula into the left atrium through the area between the right superior and inferior pulmonary veins. Blood returns to the patient through a graft sutured to the ascending aorta. For right heart support inflow is achieved through a 51F cannula in the right atrium, and the outflow graft is sutured to the pulmonary artery.

Several distinct orientations of the device were used until the final optimal orientation was adopted (Fig 1). The objective for device orientation is to eliminate the crossing of drive lines in the mediastinum to minimize dead space and the potential for mediastinal infection, as well as to decrease trauma to the skin at the drive line exit sites. Kinks in the drive lines are carefully avoided.

Device rate was adjusted to provide a stroke volume of at least 45 mL but no more than 65 mL (maximum stroke volume, 70 mL). Complete washout at device systole

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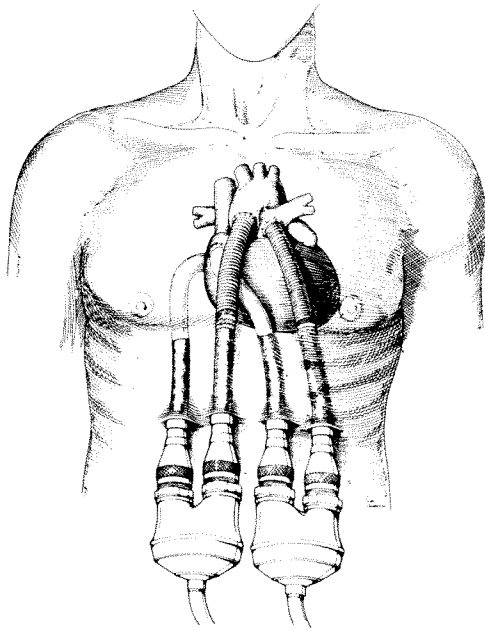


Fig 1. Current positioning of the Symbion acute ventricular assist device. Note that drawing nipples are not shown because they are on the posterior aspect with this positioning.

minimizes thrombus formation. Maximum vacuum applied was 20 mm Hg. A device rate around 80 pulsations per minute usually allows for optimal filling of the artificial ventricle. Hemolysis correlates directly with drive pressure and can be kept at less than 10 mg/dL plasma free hemoglobin with drive pressures less than 180 mm Hg.

Anticoagulation measures were used in all patients. Dextran 40 at 25 mL/h was used until heparin could be started. Dipyridamole (Persantine; Boehringer Ingelheim, Ridgefield, CT) administration was begun shortly after implantation at 50 to 100 mg orally every 6 hours and usually continued until removal of the device. When postoperative chest tube output became clear, administration of heparin was started and titrated to maintain a partial thromboplastin time at twice control value. Patients in whom long-term support was anticipated were converted to warfarin sodium (Coumadin; Du Pont Pharmaceuticals, Wilmington, DE) anticoagulation to maintain a prothrombin time of 1.5 to 2 times control.

Physical therapy was initiated immediately after implantation. Moving the patients prevented the development of areas of stasis in the artificial ventricle. Patients were generally ambulatory by the fourth postoperative day. Patients were not considered candidates for transplantation until nutritional deficiencies and other organ dysfunction, particularly renal dysfunction, were reversed.

All patients received prophylactic antibiotics directed particularly at staphylococcal organisms. After removal of the device, the mediastinum was assumed to be contaminated and administration of antibiotics was continued for a minimum of 7 postoperative days. A closed irrigation

system using dilute povidone-iodine (Betadine; Purdue Frederick Co, Norwalk, CT) for 2 to 3 days followed by normal saline solution for 1 to 2 days was used in all patients after transplantation. The irrigation system and chest tubes were not removed until culture of the chest tube drainage was negative.

Results

Our biventricular experience includes 13 patients with refractory heart failure (Table 1). Six of these patients underwent heart transplantation after 23, 65, 53, 164, 39, and 33 days of support. A seventh patient required biventricular support at the time of heart transplantation because of immediate graft failure. Her allograft recovered, and her biventricular assist device was removed after 10 days of support. Of these 7, 6 are alive and well and 1 died 2 months postoperatively due to severe acute rejection. He was not placed back on the ventricular assistance. The mean survival is 2.1 years, and the longest survival to date is 3.7 years.

The remaining 6 patients died on the device of a variety of causes after 1, 15, 4, 6, 21, and 35 days of support. Three of these patients (patients 4, 5, and 9) arrived from outside institutions critically ill due to postcardiotomy failure, on centrifugal ventricular assistance with an intra-aortic balloon pump to improve coronary flow. All 3 were placed on the Symbion within hours after arrival, and they died at 1, 6, and 15 days. A fourth patient (patient 10) was placed on the Symbion because of severe rejection of an allograft heart that he had received 48 days previously. He died of cytomegalovirus sepsis after 21 days of support. Patient 7 died of multiple organ failure precipitated by influenza B myocarditis. Patient 13 died of multiple peripheral emboli.

Seven patients had blood cultures that grew bacteria while on the device. Two of these patients' infections were clearly due to intravenous catheter sepsis (patients 8 and 13), which resolved with removal of the catheters and appropriate antibiotics. One appeared to be due to an *Escherichia coli* drive line infection (patient 11), which resolved with local wound care and intravenous antibiotic therapy. Another was the result of a mediastinal *Staphylococcus aureus* infection (patient 2). Both of these patients went on to successful transplantation without postoperative infection. The rest of the patients had isolated positive blood cultures with minimal growth (less than one colony per milliliter), some of which may have been due to contamination, none of which proved to be clinically significant (Table 2).

Of the 7 patients surviving to explantation (6 transplanted, 1 weaned), 4 had some bacterial growth from the mediastinal tissue and prosthesis samples taken upon device removal. However, only 1 patient had consistent growth from multiple samples (patient 2). All ventricular assist device conduits were well incorporated and without clinical signs of infection. All conduit material was completely removed at the time of explantation, and no postoperative infections were due to the devices. Perigraft infection did not cause major morbidity.

Table 1. Patient Profile

Patient No.	Sex	Age (y)	Weight (kg)	BSA (m ²)	Implantation Duration (d)	Hemodialysis	Indication for Implantation	Support Before Implantation	Outcome	Years Alive
1	F	56	65	1.72	10	No	Immediate transplant failure	CPB	W	3.7
2	M	40	59	1.65	23	No	Acute MI	IABP	T	3.6
3	F	40	54	1.55	65	Yes	Postpartum cardiomyopathy	IABP/BVAD	T	3.4
4	M	46	102	2.27	1	No	Acute MI	IABP/BVAD	D	...
5	M	56	100	2.22	15	Yes	Postcardiotomy (CABG)	IABP/LVAD	D	...
6	M	46	64	1.74	53	No	Idiopathic cardiomyopathy	CPS	T	0.3
7	F	42	80	1.93	5	Yes	Viral cardiomyopathy	IABP	D	...
8	M	48	110	2.36	164	No	Acute MI	IABP	T	1.7
9	M	45	80	1.99	6	Yes	Postcardiotomy (MVR/CABG)	IABP/BVAD	D	...
10	M	65	82	2.02	21	Yes	Acute rejection	IABP	D	...
11	M	49	70	1.82	39	Yes	Acute MI	CPS	T	1.1
12	F	56	73	1.82	33	No	Idiopathic cardiomyopathy	CPS	T	0.7
13	M	59	59	1.69	35	No	Idiopathic cardiomyopathy	...	D	...

BSA = body surface area; BVAD = biventricular assist device; CABG = coronary artery bypass grafting; CPB = cardiopulmonary bypass; CPS = Bard portable cardiopulmonary bypass system; D = died; IABP = intraaortic balloon pump; MI = myocardial infarction; MVR = mitral valve replacement; T = transplantation; W = weaned.

Tiny clots and "plaques" (generally ≤ 1 mm diameter) could be seen inside the ventricular assist devices through the clear housing. They appeared most frequently at the diaphragm-housing junction. These appeared and disappeared from day to day. Disappearance did not correlate with clinical emboli. This phenomenon had been previously reported [12].

Thromboembolic complications developed in 7 patients. Two patients (patients 3 and 11) suffered strokes, but nearly completely resolved their deficits. Another (patient 8) had an episode of amaurosis fugax 7 days after implantation. This corresponded to the accidental discontinuation of his heparin infusion. All 3 of these patients with apparently isolated cerebral embolic phenomena underwent successful transplantation. The other 4 patients had multisystem emboli. Two (patients 5 and 9) were transferred from outside institutions on centrifugal assist devices before Symbion placement. Two (patients 9 and 13) had clots in the left heart at postmortem examination.

Five of the 7 survivors did not require hemodialysis while on the devices (Table 3). Three of these became more "prerenal" while on the Symbion (patients 1, 6, and 12). The prerenal azotemia of patient 12 resolved once her tamponade-producing mediastinal hematoma was evacuated on day 14. Six patients (patients 3, 5, 7, 9, 10, and 11) underwent hemodialysis while on the ventricular assist devices. Their dialysis runs were generally uneventful, but fluid removal goals were often not met due to intolerance of poor venous return to the ventricular assist

devices. Two patients (patients 3 and 11) recovered renal function while on dialysis and went on to transplantation.

There was no correlation between preoperative blood urea nitrogen level and survival (Table 4). Weight did correlate with survival (nonsurvivors mean weight = 83.8 kg; survivors mean weight = 70.7 kg) (Table 5).

Comment

We have employed biventricular support almost routinely since April 1988. Early experience with right heart failure after left ventricular assist device implantation has led us to adopt this approach.

Most of our success has come in the bridge-to-transplantation setting. Our preference of the asynchronous drive mode with the drive rate set at about 80 beats/min may be in part a reflection of this experience. Whereas the *synchronous* mode may allow for better decompression of the native ventricle, the device rate is slave to the native heart rate, which is usually too fast and often too irregular for optimal filling. This limits output. Moreover, higher drive pressures are required to overcome the systolic resistance and shortened ejection periods, therefore increasing hemolysis. Thus, we favor the *asynchronous* mode. We do not expect our transplant candidates' native hearts to get significantly better after a period of ventricular assistance. We do, however, wish to reverse damage to other end-organs such as the liver and kidneys, and thus will sacrifice some cardiac end-diastolic pressure for end-organ perfusion, if necessary.

Table 2. Morbidity and Mortality

Patient No.	Emboli	Reexploration	Viral and Blood Cultures	Mediastinal Infection of Explant	Drive Line Infection	Cause of Death
1	0	0	1/10 <i>S epidermidis</i>	1+ <i>S epidermidis</i> , diphth cond strep		N/A
2	0	0	4/19 <i>S aureus</i>	3/3 <i>S aureus</i>		N/A
3	Cerebellar CVA, day 57	Day 26, decorticate left hematoma	2/80 plus <i>S epidermidis</i> , day 15, 1 streptococcus	2/11 <i>S epidermidis</i> , <i>Bacteroides</i> , left chest clot	RVAD 1+ <i>S epidermidis</i> , day 17	N/A
4	0	0	0	N/A		Hypoperfusion and coagulopathy
5	Splenic infarct, necrotic toes	0	0/13	Implant 1 + streptococcus		MOF (anuric/ARDS/ liver failure), emboli (spleen, lower extremities?)
6	0	0	0/36	0/4		Acute rejection after discharge
7	0	Day 1, bleeding	Influenza B, NP swab, myocardium 7A	NA		Influenza B viral sepsis/MOF-
8	Amaurosis, day 7	0	5/27 <i>S aureus</i> , days 19-22	1/7 <i>S epidermidis</i>		N/A
9 ^a	Kidney right and left spleen infarct	0	0/5	Implant <i>S epidermidis</i>		Cardiac emboli (kidneys/spleen)
10	Splenic left renal infarct	0	CMV	CMV		CMV sepsis (heart, lungs, esophagus, bowel, urine/liver) and emboli (spleen, left kidney)
11	Pontine lesion, day 29	0	1/16 day 28, <i>E coli</i>	Negative	<i>E coli</i> , day 26	N/A
12		Day 13, evacuate clot	1/5 Diphtheritic	1+ <i>Enterobacter</i> ; reexploration for bleeding	1+ <i>Enterobacter</i>	N/A
13 ^a	Cerebral CVA ×2, splenic renal right and left infarcts	0	3/21 2 <i>S aureus</i> , <i>S epidermidis</i>	Negative		Cerebral emboli (occipital-parietal cortex/spleen/ kidneys)

^a Left ventricular and left atrial clots at postmortem examination.

ARDS = adult respiratory distress syndrome; CMV = cytomegalovirus; CVA = cerebrovascular accident; MOF = multiorgan failure; N/A = not applicable; NP = nasopharyngeal.

Table 3. Renal Function of Survivors Not Dialyzed

Patient No.	Preop BUN (mg/dL)	Preop CR (mg/dL)	Preop BUN/CR Ratio	Maximum BUN (mg/dL)	Maximum CR (mg/dL)	Maximum BUN/CR Ratio	Worst Renal Function on VAD Day #
1	17	0.9	19	72	2.0	36	4
2	54	2.0	27	60	2.1	29	21
6	21	1.0	21	120	1.8	35	51
8	65	1.6	40	112	6.2	18	5
12	23	1.7	13	81	1.5	49	13
Average	36	1.4	25	89	2.7	33	19

BUN = blood urea nitrogen; CR = creatinine; VAD = ventricular assist device.

Table 4. Preoperative Blood Urea Nitrogen and Survival

Nonsurvivors Preop BUN (mg/dL)	Nonsurvivors		Survivors Preop BUN (mg/dL)	Survivors Preop Creatinine (mg/dL)
	Preop Creatinine (mg/dL)			
30	2.6	17	0.9	
17	1.5	54	2.0	
18	1.9	16	0.6	
32	1.2	21	1.0	
79	2.6	65	1.6	
15	1.1	19	1.1	
		23	1.7	
Average = 32	Average = 1.8	Average = 31	Average = 1.3	

BUN = blood urea nitrogen.

Emergent placement of the biventricular assist devices has not, by itself, been a risk factor in properly selected patients. Three patients awaiting transplantation were placed emergently on the Symbion after bedside stabilization with the Bard CPS portable cardiopulmonary bypass system. All 3 underwent successful transplantation (patients 6, 11, and 12). On the other hand, none of the 3 who arrived from outside institutions on centrifugal devices after cardiectomy survived. In retrospect, these patients were not good candidates based on their initial conditions and delay in arriving at our institution.

We have tried not to use the Symbion in patients who weigh more than 80 kg because of the limited output of the device (approximately 5 L/min). In larger patients, we favor a total artificial heart. Body surface area and preoperative blood urea nitrogen level did not correlate with

Table 5. Body Surface Area and Weight

Body Surface Area (m ²)		Weight (kg)	
Survivors	Nonsurvivors	Survivors	Nonsurvivors
1.72	2.27	65	102
1.65	2.22	59	100
1.55	1.93	54	80
1.74	1.99	64	80
2.36	2.02	110	82
1.82	1.69	70	59
1.82		73	
Average = 1.74	Average = 1.85	Average = 70.7	Average = 83.8

survival, but weight did. However, 3 of the 6 nonsurvivors arrived recently after a cardiac operation in an edematous state, and this may not be a true reflection of their dry weight. Moreover, our longest-supported survivor (164 days) weighed the most (110 kg).

The Symbion acute ventricular assist device has been reliable and durable for our use, which has been predominantly in the bridge-to-transplantation setting. Although infection, hemolysis, and thromboembolism have been associated with the device, none have ultimately limited its usefulness. Proper patient selection requires exclusion of those with preexisting multiple end-organ failure (but not isolated renal and cardiac failure) and intracardiac clots, and possibly those with large body size.

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Nursing Care of the Patient on Mechanical Circulatory Support

Moderator: Julie A. Shinn, RN

Panelists: Nancy Abou-Awdi, RN, S. Jill Ley, RN, Jane E. Reedy, RN, and W. Donald Rountree, RN

MODERATOR SHINN: In the not too distant past, nursing care of the patient on circulatory assist was part of the "heroic" measures taken to save a patient who could not be weaned from cardiopulmonary bypass. In the last decade, we have witnessed the development of many devices capable of successful postcardiotomy support and long-term support for waiting transplant candidates. The latter group of patients are no longer strictly critical care patients, but actually can recover from severe heart failure or shock with the support of these devices. Those are some of the issues we would like to discuss today.

We have a distinguished panel of nurse experts, all with extensive experience in circulatory assist. To my right is Nancy Abou-Awdi, RN, who is a Clinical Research Coordinator at the Texas Heart Institute in Houston. Seated to her right is Jill Ley, RN, a Cardiovascular Clinical Nurse Specialist at the California Pacific Medical Center here in San Francisco. Jane Reedy, RN, is well known to anyone active in circulatory assist. Jane is a Clinical Nurse Specialist from St. Louis University Medical Center. And the fourth member of the panel is Donald Rountree, RN, who is a Critical Care Clinical Nurse Specialist from the Humana Hospital-Audubon in Louisville, Kentucky.

Each panelist has prepared a brief address on a separate topic. After the four topics have been presented, we will open up the floor for discussion. Because these topics are all so closely related, we elected to hold our discussion on the care of the long-term patient until the end of the session.

Our first speaker will be Nancy Abou-Awdi, RN, and she will address the transfer of ventricular assist device patients to non-critical care areas.

MS ABOU-AWDI: The therapeutic objective for ventricular assist device (VAD) patients is to support hemodynamics until either recovery of the native heart occurs or a donor heart can be found. Currently, numerous patients are listed for transplantation, and this has considerably lengthened the wait for a donor, sometimes beyond a year. Management objectives of VAD patients have changed to incorporate not only the critical care needs of the acutely ill, but also rehabilitation needs of a patient recovering from cardiogenic shock. Thus, it has become appropriate to consider housing these patients outside of critical care units.

Currently in the United States, there are four systems

being used to support long-term patients who do not require constant critical care. They are the Pierce-Donachy by Thoratec, the Novacor left ventricular assist system, and two HeartMate systems, an implantable pneumatic and a vented electric system. Why do we need to transfer these patients? The main reason is that patients eventually do not require critical care. They reach a point where they are no longer in unstable condition, they do not require pharmacological agents, and there is no further need for the skills of critical care nurses. The other important factor, and probably primary at our institution, is that the psychological stress of being in critical care more or less inhibits patient recovery. If we look at the cost-benefit issue, there is a major difference in the cost of care in a critical care unit versus the general floor. Cost-benefit is something that we are all very concerned about these days.

So what are the criteria for transferring a patient? I did a survey of several centers with my colleagues and we came up with four basic criteria.

Patients considered for transfer must be in hemodynamically stable condition and not be requiring pharmacological support of hemodynamics. It is also important that patients are taking a majority of their calories orally and tolerating their diet. Finally, patients should be ambulatory. The rehabilitation process begins with muscle strengthening of both upper and lower extremities. Patients progress to daily exercise on an inclined treadmill for up to 30 minutes per session. Before we began transferring patients out of critical care, we kept an active patient such as this for months in a critical care unit.

A major key to successful transfer is preparation of the nursing personnel on the general care unit. The idea of accepting a patient on circulatory support to a general care area conjures up visions that are quite frightening to staff who have never cared for such a patient. Staff preparation will vary from center to center. The support personnel are somewhat different, and the nurses function in different ways. Basically you need to provide staff with knowledge about the device. How does it work? What do I do if? They need to know what to do and what not to do in emergency situations. For example, these patients still have end-stage heart disease and will likely have dysrhythmias. Staff need to understand how dysrhythmias might impair pump output and how to respond. Each center has an educational program for their staff. Some are more elaborate than others, but the primary goal is to

develop a staff that is well prepared for any situation they might encounter with these patients.

Usually a simulator for the device or a mock circulatory loop is set up so nurses and circulatory support personnel can get "hands-on" practice. We can simulate various situations so that staff become very comfortable with the system and know what to do if any emergency arises. St. Louis University uses a detailed self-study program for the two systems they use. The self-study addresses the physiologic response as well the function and operation of the consoles. Most of these patients are totally rehabilitated by the time of transplantation. They also need to know about their systems. Most of them are very curious about what to do if anything should happen with their console. So we have taught the patient and a family member how to work the console and how to switch consoles if need be. They know how to use the manual back-up systems and who to call for help. Pittsburgh has taken this same approach with patients and families.

In conclusion, the actual process of transferring VAD patients is simple. The necessary steps to address in your institution before implementing this change are establishing guidelines for transfer and setting up an education program for all personnel involved in the transfer and care of the patient. The next step, as I see it, will actually be discharging these patients from the hospital. Two of my current patients at Texas Heart Institute have been in the hospital 75 days and 110 days and they are ready to get out. They both know more about their devices and how they work than most of the personnel in the hospital.

MODERATOR SHINN: Our next speaker is Ms Jill Ley, from California Pacific Medical Center in San Francisco. She will address the topic of nutritional support and activity guidelines.

MS LEY: The benefits of nutritional intake are now very well documented in terms of reversing protein catabolism, improving wound healing, and promoting immunocompetence. Questions remain, however, as to what to give and how much to give. To answer these questions for VAD patients, one can begin with a nutritional assessment. Traditional measures of nutritional adequacy include estimation of ideal body weight based on standardized height/weight tables and anthropometric measures of mid-arm circumference. These measures, however, can be grossly inaccurate in the cachectic patient in need of diuretic therapy. Once you add about 10 pounds of hardware to the patient, their ideal body weight becomes anybody's guess.

Assessment of caloric requirements has traditionally relied on standardized equations. Our dietitians use the Harris-Benedict equation and factor in components of weight, height, and age to arrive at ideal caloric requirements for our patients. It can be adjusted for physiologic stress, which will more optimally predict the true caloric needs of patients who are critically ill. A newer method is indirect calorimetry, which determines O_2 consumption and CO_2 production. This method allows you to get a more accurate estimate of patient's true caloric needs. I

mention it because we used this technique in one of our patients. It can be done at the bedside in either spontaneously breathing patients or patients who are ventilated. The test takes a period of 15 to 20 minutes. We found something very interesting when we did one of these metabolic studies on a patient who was on a ventricular assist device 3 weeks after implantation. The patient was extubated and ambulatory at the time. The patient's basal energy expenditure was approximately 12.8% lower than had been anticipated. The dietician noted that under normal circumstances the metabolic requirements of a normally functioning heart are approximately 9.2% of your basal metabolic requirements. So it was speculated that perhaps in patients who have devices taking over myocardial function, we may be overestimating their caloric needs. We have not had a chance to repeat this in another patient yet, so I cannot tell you whether or not we will find this in multiple patients. But I thought it was of note.

Once you have calculated caloric needs, actually getting your patients to take in those calories becomes the true battle. It makes sense to try to use the gastrointestinal tract. Recent work has indicated that using early enteral feedings protects the gut flora and the lining of the gastrointestinal tract and can reverse or at least stop the deterioration or atrophy of the gut that occurs in patients who have been hypotensive or in shock. That may in turn prevent septic episodes by maintaining the homeostatic barrier within the gastrointestinal tract. One of the questions I would like to raise for later discussion is whether anybody is using selective gut decontamination protocols with oral antibiotics to maintain gut homeostasis.

I would like to highlight a report from Ms Abou-Awdi's group in Houston. Vega and associates evaluated nutritional intake in 9 patients with left VADs. In these 9 patients, they found that virtually no patients were meeting 100% of their intake by parenteral methods. In addition, when they looked at these data using a scale to evaluate nutritional deficits, 4 of 9 patients were deemed moderate to severely undernourished early after VAD placement. When they later repeated these values, they found that almost all of their patients were able to meet close to 100% of their caloric and protein requirements. Four of these patients were doing that with diet alone. Diet is clearly the preferred method we would like to use to meet nutritional needs.

One problem that interferes with nutritional intake in VAD patients with implantable devices is the feeling of early satiety, even with small meals. Several interventions have been recommended for these patients, including smaller meals and spacing them out more during the day so that patients are able to get adequate intake. Getting your patients away from the hospital room to an area where they can have some privacy and eat in a relatively normal fashion can significantly promote dietary intake. I do not have any data to support this, but common sense says that patients in a more normal environment would be more inclined to eat better. Patients can eat anything and everything they want in our institution. We discourage salt use if they are having problems with failure, but

generally that is not even a problem. Oftentimes patients like beer or wine with meals and we encourage that. We also encourage families to bring food in from home or to order out for favorite foods.

For patients having difficulty meeting nutritional needs with diet alone, most centers are inclined to go with enteral feedings first. This method can provide a tremendous amount of caloric intake. One technique we have used for patients with inadequate oral intake is nocturnal feedings. We might give continuous tube feeds from 8 PM until 6 AM. Patients can get as much as 50% of their caloric requirements with this technique. They are also not so full during the day that they cannot eat a normal diet.

Next I would like to address mobilization of VAD patients and start by pointing out that there is a tremendous spectrum of patients that you will see. How mobile you get these patients is clearly dependent on what type of patient you are starting with. On one extreme, you have the patient with an open chest covered with a Silastic patch and an external device. No one will be anxious to be too aggressive with that patient. Protocols for this type of patient will center around tilting or turning every 2 hours and passive range of motion exercises. A device such as the Johnson & Johnson Hemopump will also restrict aggressive mobilization. The device requires femoral arterial cannulation, which necessitates restriction of hip flexion.

In patients who have implanted devices, you can get much more aggressive with activity. The exercise protocol used in St. Louis mobilizes patients very early. In the first 24 to 48 hours after implantation, patients are turned every 2 hours and range of motion is started. During the intermediate period out to about 5 days, patients begin to get up in a chair. They have had a couple of patients who were actually ambulatory this early. Their earliest patient started ambulating 3 days after VAD implantation. Telemetry pouches are used to support the devices. With the help of encouraging nursing personnel, they are able to consistently get their patients up and moving quite early. Longer-term patients are progressed to stationary bike riding and ambulating with their devices. Patients can begin the more vigorous conditioning with bedside cycling exercises. We have used this technique for conditioning before getting patients up for the first time. It is similar to the way patients are exercised during a cardiac catheterization study. Patients with implanted devices can actually go to a physical therapy suite, get on treadmills, and use other types of exercise equipment.

One caution to keep in mind is that of all these patients have healing sternotomies, and it is important to avoid using upper extremity weights. Our standard sternal precaution protocol restricts lifting more than 5 to 10 pounds for 4 to 6 weeks.

In conclusion, I think future research could address some of these issues I have discussed. A few primary questions are what is the effect of nutrition and aggressive mobility protocols on length of stay or on infectious complications? And how far can we safely go in mobilizing patients on centrifugal devices?

MODERATOR SHINN: I would like to acknowledge and thank Jill Ley for playing a major role in planning this nursing session. Our next topic is infection control measures, which will be presented by Jane Reedy from St. Louis University Medical Center.

MS REEDY: The major infection control measure used at St. Louis University Medical Center is good hand washing. Many years ago, we used reverse isolation and found that it really did not affect the infection rate. So now we simply emphasize good hand washing and meticulous sterile dressing changes. Intravenous sites are changed every 4 days, and tubing changes are made every 2 days. Of course, another important strategy is to get the patient extubated as quickly as possible.

The antibiotic protocol used at St. Louis University includes a cephalosporin if patients have no preoperative infection and have been in the hospital less than 5 days. An aminoglycoside is added if they have been in the hospital greater than 5 days. If patients have had a preoperative infection, the preoperative antibiotic regimen is continued. Administration of these antibiotics is discontinued when our infectious disease team believes it is appropriate. Prophylactic antibiotic administration is stopped after 3 days if there is no clinical sign of infection. Cultures for blood, urine, and sputum are obtained for any temperature greater than 38.3°C. Only clinically significant infections are treated. Obviously, if the patient is in septic shock immediate antibiotic coverage is started. For a superficial wound infection or a fever, we try to wait for culture results before beginning antibiotic therapy.

Within 24 hours of device insertion, VAD dressing changes begin every 8 hours and are cut back to every 12 hours once the drainage has stopped. Site care consists of normal saline cleansing, Betadine spray, and dry dressings applied to the cannulas or drive line site. At the Texas Heart Institute, silver sulfadiazene creme is used after cleansing with half-strength hydrogen peroxide. Currently, Thoratec does not recommend using hydrogen peroxide because of concern that it might affect the integrity of the cannula. At California Pacific Medical Center, dressings are changed twice a day for 4 days, then every other day. A one to ten strength Hibiclens and normal saline solution is used to cleanse the VAD sites. A Kerlex sponge dampened with the solution is packed around the sites. Sites are then covered with an ABD dressing and secured with Montgomery straps. They have had good luck preventing drive line infections with this technique.

Our surgeons place retention sutures around the cannulas or drive line. Sutures are routinely removed at day 7. The retention sutures are a nice idea because they immobilize the cannulas, and this helps to promote good tissue ingrowth around the VAD sites.

One of our patients was supported on a Novacor system for 370 days and had good tissue ingrowth. An infection did not develop in this long-term patient until day 365 of VAD support. It was a superficial *Staphylococcus aureus* infection. He underwent transplantation 5 days later with no postoperative complications. Many of our

patients have some tracking along the drive line or cannulas. In this situation, we cleanse around the site and along the track with a Q-Tip moistened with normal saline solution. It is very important to cleanse down the track and remove all debris. Irrigations with a suction catheter and normal saline solution can be used for deep tracking (>2.5 cm). Good wound cleansing with antibiotic irrigation when local infection is present can forestall the need for antibiotic coverage. Adequate immobilization of the cannula site is important for prevention of drive line infections as well as encouraging tissue ingrowth.

Most of our drive line infections occur in patients who are on the device for longer than 30 days. I would like to discuss 10 of our patients who were on a VAD for longer than 30 days. All 10 patients suffered from end-stage heart disease. Age ranged from 27 to 56 years (mean, 46 years). Duration of VAD support was from 31 to 440 days (mean, 130 days). Drive line or cannula infections developed in 7 of the 10 patients. The infections were primarily *Staphylococcus aureus*. Five of the 7 patients with drive line or cannula infections had development of positive blood cultures and 2 patients also had development of a mediastinal infection. The first positive cultures were obtained 10 to 364 days (mean, 71 days) after device insertion. The percentage of time on antibiotics ranged from 7.8% to 97% of the duration of VAD support. One of the 10 patients supported for longer than 30 days died. However, his death was not related to infection. One patient with a mediastinal infection was weaned from the device after ventricular recovery and discharged from the hospital. Five of the 8 patients who received transplants had a previous infection. Seven of the 8 patients who received transplants were discharged from the hospital. The non-survivor was a woman who had been supported with a Jarvik total artificial heart for 440 days and was on antibiotics 97% of the time for a drive line infection. Mediastinitis was discovered at the time of transplantation. She remained on antibiotics for several months after transplantation before dying at 3 months of renal insufficiency and infectious complications.

Another concern with implantable devices is the potential for pocket infections. Jackson-Pratt drains are used immediately after insertion of the Novacor VAD. In one particular patient, the drain was not discontinued until day 6 after operation. The site was reddened and never healed completely. About 3 weeks after the device was implanted, a fever developed. An incision was made at the old Jackson-Pratt site and purulent drainage was found. The patient was taken to the operating room, and his Novacor pump pocket was opened. *Staphylococcus aureus* was cultured from the site, and 2 weeks of antibiotic coverage was required to sterilize his blood. He remained on intravenous antibiotics until transplantation. Vancomycin wound irrigations were used, and there was evidence of some tissue healing before transplantation. His blood culture had been sterile for 3 weeks when a heart became available, so he underwent cardiac transplantation. *Staphylococcus aureus* and *Candida* were cultured from his pump inflow cannula. He was treated with a 6-week course of amphotericin and vancomycin. Four

weeks after transplantation, he was sent home with a Hickman catheter. The patient went back to work as a secret service agent 3 months after transplantation and was Dan Quayle's bodyguard during the presidential elections in 1988.

Some infections associated with VAD support can be quite terrible but can be controlled with antibiotics and aggressive dressing changes. The patient just discussed had VAD dressing changes every 4 hours until transplantation.

In conclusion, infections are common in patients supported greater than 30 days. If an infection can be controlled, successful transplantation is possible. Multiple antibiotics or antibiotic therapy required for greater than 3 months is associated with reduced chance of survival. *Staphylococcus aureus* is the most common drive line infection that we have encountered in our patient population.

MODERATOR SHINN: Our last panelist is Donald Rountree from Humana Hospital in Louisville, Kentucky. He will discuss psychosocial aspects of care.

MR ROUNTREE: We have made major strides in our knowledge base over the past few years. Our nursing management of these patients has certainly had a major physiologic focus. What I will talk about for the next few minutes is the psychosocial aspects of patient care. I am a very strong believer that there is not a more appropriate health care provider to address the patients' psychosocial problems than the critical care nurse or the nurse in general. When one looks at the literature regarding nursing problems associated with patients on VADs, two problems are mentioned repeatedly. One is anxiety- or fear-related issues and the second is ineffective coping on the part of either the patient or the family. All of the nursing literature related to mechanical circulatory support certainly addresses these two issues. Because there is such a diversity of devices and lengths of support, I advocate that we divide the psychosocial aspects of care into two stages.

First, I will discuss the short-term patient or the patient in the acute stage, followed by the longer-term patient or the patient in the chronic stage of support. I think you will find some distinct differences in the psychosocial issues depending on what stage those patients happen to be in.

In the acute phase of support, the primary focus is the family. Many of these patients are intubated or sedated, or they may even be paralyzed. Therefore, it is the family that is either going through anxiety-related issues or not coping very well. Our major focus needs to be with the family in the first stage. In the longer term phase, or what I call stage two of support, our focus needs to switch and be more geared to the patient. These patients are up, ambulating, eating, exercising, and some are even leaving the hospital.

In the acute phase of support, anxiety and fear are certainly major. There are two reasons why anxiety and fear are very common. Number one, the device is placed as the result of a life-threatening or emergent situation. A most common reaction of the family during this time is to

be fearful or to be very anxious. So our interventions focus on the family. The other reason we have anxiety- or fear-related problems in the acute phase is that there is knowledge deficit. The patient being bridged to transplantation is a little different because during their evaluation they are told of mechanical assistance and the possible need for mechanical assistance. So they, very possibly, are better prepared. In the acute myocardial infarction patient or the postcardiotomy shock patient, it is the family that generally gives consent for the device to be placed. Even though the procedure and the insertion may have been talked about by the nursing staff, what the family actually comprehends during this preinsertion stage is usually very limited. So both knowledge deficit and a near life and death situation exist, which certainly produces anxiety and fear. The second problem seen in the acute phase is an ineffective coping pattern. The degree of this depends partly on the functional level of the family. We deal with a variety of patient populations and a variety of families. Certainly the functional level of the family determines how well they are going to cope with this situation. There are also some factors in the acute phase that certainly contribute to ineffective coping and anxiety. One is possible feelings of hopelessness on the part of the patient and the family. Impaired communication is another factor. Many of these patients remain intubated for several days. There may be some alteration in family function precipitated by the patient's illness.

Most of the time, interventions during the acute phase are simple but important. I just want to highlight some that are particularly important. Number one, nurses need to demonstrate good communication skills and be sensitive to the patient and the family. Allow the patient, if possible, to express fears and concerns. Another important intervention during this time is regular daily conferences with the family. It is vitally important that they be kept informed. I really want to stress the importance of adopting an attitude of honesty and cautious encouragement. In other words, you can be hopeful while being realistic. Providing the family with alternative support systems such as clergy and social services can help provide them with some means to identify coping strategies.

In the long-term phase, anxiety and knowledge deficit will continue to be issues. The focus at this time centers on the patient. A very important issue to address in the long-term patient is a potential sense of powerlessness. There is a very limited amount in the nursing literature regarding this concept. By definition, powerlessness is a state in which the individual perceives a lack of control. There are two major reasons why powerlessness is a very appropriate nursing diagnosis during this long-term phase of support. Number one, there is an uncertainty or a lack of control over when the donor heart will be located. We are seeing longer and longer periods of support until transplantation occurs. Second, patients can develop feelings of powerlessness because they are on a machine to sustain life. Although the majority of the devices are very reliable, there is always the potential for malfunction. Also, patients are hospitalized for an extended period of time. Powerlessness is also related to an

individual's locus of control. The degree of powerlessness may be influenced by whether an individual has an internal or external locus of control. As you know, a person who displays internal locus of control motivates himself and feels like he can control his fate, whereas somebody who has an external locus of control really needs to be motivated by others because he feels what is happening to him is the result of someone else or fate. How severe a patient displays powerlessness may depend on his locus of control. Many patients experiencing powerlessness will exhibit anger, sadness, apathy, or even hostility. Some may have periods of frank depression. Distorted perceptions of reality and withdrawal from activities may be other signs.

So what do we do for these patients? First, we try to eliminate or reduce any contributing factors. The second thing to do is to provide opportunities for the individuals to control their own environment. Interventions include allowing them to sleep at night, extending visiting hours, and maybe providing consistent staffing patterns. Let the patients make some decisions about their care. It is important to determine what kind of locus of control each patient has. If a patient has an external locus of control, then motivate him to make some decisions. If the patient has an internal locus of control, provide him with information that will help him make decisions regarding care. Increasing the patient's knowledge base with teaching and referrals to appropriate sources of information can help to counterbalance their sense of powerlessness or hopelessness. Many patients enjoy becoming very knowledgeable about their devices.

So, in conclusion, the focus of nursing interventions will change as the patient progresses from the acute to chronic stage. The four major nursing diagnoses that will likely be encountered throughout are anxiety, fear, ineffective coping, and powerlessness.

MODERATOR SHINN: We would like to open the session up for discussion. Please identify yourself.

PAM BRUEM (Portland, OR): I want to thank the panel for making sure that this meeting had a nursing section in it. I really appreciate that. At our hospital our team is very involved in the acute phase. I would be interested to hear about the various roles that nurses play in the long-term phase: research, clinical nurse specialists, managers. What are some of those roles, and how are different nurses functioning in these roles?

MS ABOU-AWDI: The role that I have is clinical research coordinator at Texas Heart Institute. The role is really a mixed bag. I am Master's prepared and I have been working in the laboratory for 3 years. My original position required data collection, obtaining informed consent, and going with the patient to operation to document various things that went on. But over time, this position has greatly expanded. The patients more or less demand it. They want to identify with someone who is responsible for the clinical trial, as well as ongoing care. I also participated in changing nursing procedures and policies

so that these patients can be transferred, are able to walk outside of the hospital, go to the cafeteria for their meals, and go to physical therapy. I am still responsible for the entire clinical trial.

MS BRUEM: What do other nurses do on your team?

MS ABOU-AWDI: I am the only nurse on my team. I work at the Texas Heart Institute, which is separate from St. Luke's Episcopal Hospital. The patients on the devices are inpatients at St. Luke's Episcopal Hospital. The primary care givers are the nurses on the transplant unit, either in the coronary care unit or the general transplant floor.

I work very closely with the clinical nurse specialists on the transplant service, and together we devise the protocols to increase the patient's activities over time.

MS LEY: I will just address that real quickly. I am a clinical nurse specialist, and my role starts when we find out a patient is going to have a VAD implanted. Usually it is the family that has given consent, so I meet with the family and give them as much information as they can handle at the time. My role really focuses on keeping them informed, updated, and educated. And the people who work very, very well with the patient are the bedside nurses. We use a primary nursing model, and we have had no problem whatsoever having people volunteer to be primary nurses for these patients. They coordinate care conferences and work out activity schedules for the patients. We usually have very consistent nursing care. It is the bedside nurses who really coordinate those aspects of care for patients.

MS REEDY: We have four members on our circulatory support team. There are two nurses, a biomedical engineer, and a senior research assistant. Once referral is received, we evaluate the patients to see if they are suitable VAD candidates and then confer with the physicians. We are in the operating room when the device is inserted to operate the console and make sure the operating room nurses are comfortable with all the equipment needed for device insertion. When the patient arrives in the critical care unit, we are there for 24 hours or until the patient's condition stabilizes to monitor the console and patient's condition. After that we are available on an "on call" basis. The nurses are trained to monitor the console and provide initial trouble shooting for a console failure. We also make sure that physical therapy starts, medications are ordered properly, and the patient's postoperative course is as smooth as possible. Nursing and patient education is also a major role in our jobs.

MR ROUNTREE: I am mainly involved with the acute stage. Because we use the Hemopump device and centrifugal pumps, I am usually involved with family contact. I go to the operating room and spend time with the critical care staff. I am the major liaison between family and the nursing staff.

CHRIS THOMPSON (Minneapolis, MN): At the Minneapolis Heart Institute we have a variety of devices, five or so now. I think if we bring another device to our nursing staff they are going to throw their hands in the air. How do you keep your nurses excited and interested in keeping up with all these devices?

MS REEDY: We provide inservices twice a year for the nursing staff and have developed a self-study packet that the nurses can go over themselves. As far as how to keep the nurses excited, I do not think they get worked up with the different devices. I think it is very routine for them. They do not really get frustrated, and they do think it is exciting. I do not think motivation of the nurses is a problem at our institution.

MODERATOR SHINN: I would like to ask a question of the group, to whoever, related to the exit site of the cannulas. Do you think that the angle of the exit site has anything to do with the incidence or the frequency of cannulation site infection? I was interested to see the upward angle of the Novacor exit site for the cannula in the St. Louis patient. At Stanford an approximate 45-degree angle downward is used. Would any of you comment on that?

MS REEDY: I cannot say that we have seen a difference in infection. We have seen a difference in patient comfort. There have been a few times when the VADs came out at a strange angle and we had a hard time keeping the pumps supported when the patient got out of bed. The patients may have more pain with certain cannula and drive line positions. It usually occurs when the cannula is coming out at almost a right angle from the body. Some of our earlier patients had cannulas that laid very parallel to the chest, and we did not have that difficulty.

JULIE COLLINS (Oakland, CA): I wanted to add a comment about infections in general. Even though we do see some infections from percutaneous lead sites, that still only represents maybe 5% or 6% of all the infections that are reported in patients on our device. About half of those infections considered device related are from the percutaneous lead, and they tend to be very superficial infections. We have had 4 or 5 patients who have had pump pocket infections that required opening for cleansing and drainage. None of those infections that were device related precluded a patient from getting a transplant. All have been managed successfully. The other question I had for Ms Abou-Awdi was, what are your protocols for who needs to stay in house to handle emergencies for patients on the floors? Is it the staff nurses or do you have a clinical engineer on call 24 hours who handles that?

MS ABOU-AWDI: Basically, it is the nurses at the bedside who do most of the initial trouble shooting. If there is truly a malfunction of some sort that they cannot handle, we have 24-hour circulatory support. It's what we call the "balloon team." They are there for balloon inser-

tions, removals, and cardiac outputs, so they are the first line of defense beyond the staff nurse. We also have research personnel on call 24 hours a day. A back-up console is available for every patient, and the consoles can easily be switched.

BARBARA TYE (Philadelphia, PA): Do you all use gut decontamination, and have you found there is a decreased incidence of infection, bacteremias, or even cannula infections as a result?

MS LEY: Actually, we do not do that with our hearts, but our liver transplant patients have been on a bowel preparation protocol. It is neomycin and mycostatin. There is some work going on with glutamine, an amino acid, that could be added to total parenteral nutrition solutions and facilitate maintaining the gut barrier. But we have not currently started that.

EDITH CLOTH (Denver, CO): What you do when a patient is placed on a device in an emergency situation and the patient ends up not being a candidate for transplantation and is not able to be weaned off the VAD?

MS ABOU-AWDI: The only VAD we use emergently is the Bio-Medicus pump for right or left or biventricular assist. With the HeartMate, the only candidates are bridge to transplantation patients, so if we do not have transplant approval, the device does not go in.

MS LEY: Unfortunately we have been in this position where a device has been placed in a patient and something happens during the period of support that makes the patient an unsuitable candidate. It is a very difficult decision. If you are dealing with renal failure, that is not a contraindication in our institution. We have performed transplantation in 3 patients who were requiring dialysis. Two of them reversed. So we do go ahead and treat specific organ dysfunction. If you are dealing with a brain dead patient, then you are certainly not doing that patient and family any favors by keeping the patient alive. In that situation, there is a team conference where the physicians meet with the family. I think what is really critical is that they understand the reality of the situation. It is a very difficult decision if the patient is deemed to no longer be a candidate. Usually these have been patients with multisystem failure or patients who were essentially brain dead.

Ventricular Assist Devices and Total Artificial Hearts: A Combined Registry Experience

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Data submitted voluntarily to the combined registry for the past 6 years on the use of ventricular assist devices for postcardiotomy cardiogenic shock in 965 patients and for circulatory support in conjunction with cardiac transplantation in 544 patients were analyzed. Of those patients whose ventricular function was expected to recover, approximately 45% were weaned from circulatory support and 25% were discharged from the hospital. Weaning status and hospital discharge were not different regardless of the type of original operative procedure or the pump design used. In the potential cardiac transplant group, 69% ultimately underwent transplantation and

66% were discharged from the hospital. The demographics (age and sex) of this group parallel those of patients undergoing isolated cardiac transplantation, and the 1- and 2-year survival estimates for patients requiring only univentricular support were equivalent to those of patients having isolated orthotopic cardiac transplantation. Ventricular assist devices are able to provide reasonable and safe circulatory support in both the postcardiotomy cardiogenic shock and the bridge-to-transplantation applications.

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For those individuals who are not familiar with the registry, approximately 6 years ago under the auspices of the American Society for Artificial Internal Organs and the International Society for Heart Transplantation, a registry was formed for the clinical use of ventricular assist devices and the total artificial heart. This particular registry is voluntary and has allowed the development of a very large computerized database, which is hopefully representative of general clinical experience. This report encompasses information gathered over the past 6 years in a rather detailed form on the clinical application of these devices in postcardiotomy cardiogenic shock and in conjunction with cardiac transplantation.

Postcardiotomy Cardiogenic Shock

Postcardiotomy cardiogenic shock requiring aggressive mechanical circulatory support occurs in somewhat less than 1% of all postcardiotomy patients. The database referable to this problem, as of December 31, 1990, consisted of 70 reporting centers, 44 of them in the United States and 26 outside the continental US. Of the 965 total applications of devices reported to the registry, 71% were in male patients having a mean age of 56 years. Twenty-nine percent of the patients were female, with a mean age of 53 years. This certainly reflects the male prevalence of coronary artery disease. Circulatory support was provided in these patients for approximately 4 days regard-

less of whether isolated left, right, or biventricular support was used. However, the wide ranges of support times (0 to 69 days) would indicate the necessity for support systems to have some short- to intermediate-term capabilities. Interestingly and without an apparent explanation, patients who were supported with vortex or centrifugal devices were weaned on an average of about 3 days, versus 6 days for those supported with pulsatile devices. There were no statistically significant differences in the mean duration of circulatory support between those patients who were weaned, not weaned, or weaned and discharged from the hospital. However, in approximately 90% of the patients who survived, circulatory support was able to be discontinued by 1 week postoperatively.

If one takes into account the nature of the original operative procedure, statistically the weaning status and hospital discharge rates were not different. Ultimate survival varied from a low of approximately 14% associated with double-valve replacement with or without myocardial revascularization to a high of nearly 30% seen with isolated coronary artery bypass grafting, which represented 53% of device use. Because statistically weaning and discharge rates did not seem to depend on the original operation, the results were analyzed by the type of support, univentricular right or left versus biventricular (Table 1). Four hundred ninety-four patients received univentricular left ventricular support and about 51% of those patients were weaned. One hundred thirty-seven, or 28%, of those patients in whom the device was implanted were ultimately discharged from the hospital. Nearly 39% of those patients receiving isolated right ventricular support (most of these patients had intraaortic balloon pumps as well) were weaned from the devices and about 26% of those patients in whom the device was

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Table 1. Overall Results of Ventricular Assist Pumping in Postcardiotomy Cardiogenic Shock

Type of Support	No. of Patients	Weaned	Discharged
LVAD	494	254 (51.4%) ^a	137 (27.7%)
RVAD	121	47 (38.8%)	31 (25.6%)
BVAD	350	132 (37.7%)	69 (19.7%) ^b
Total	965	433 (44.9%)	237 (24.6%)

^a $p = 0.0$ by χ^2 analysis. ^b $p = 0.027$ by χ^2 analysis.

BVAD = biventricular assist device; LVAD = left ventricular assist device; RVAD = right ventricular assist device.

implanted then survived to hospital discharge. Three hundred fifty patients received biventricular support, with 38% of the patients being weaned and 20%, clearly a lower number as compared with isolated support, ultimately discharged. The overall results would therefore indicate that nearly 45% of the patients were weaned from support and 25% of those patients in whom the device was implanted ultimately were discharged. Statistically a higher proportion of those patients receiving univentricular support were weaned with a significant difference and trend toward overall diminished survival with biventricular support. This is easily understood in terms of the severity of the underlying pathology. When outcome was analyzed by pump design in the postcardiotomy application, twice as many patients were supported with the more readily available and clearly less costly nonpulsatile centrifugal devices. In fact, the weaning and hospital discharge rates were not statistically different between the pulsatile and centrifugal devices.

Although the overall hospital mortality rate was about 75%, in those patients discharged, 2-year actuarial survival averaged 82% and did not statistically differ by the type of support originally used. Most importantly, in those patients who survived to hospital discharge, 86% were New York Heart Association functional class I or II.

Complications during assist pumping were common, with multiple complications recorded in individual patients. Univariant analysis indicated that bleeding, disseminated intravascular coagulation, renal and biventricular failure, cyanosis secondary to an unrecognized patent foramen ovale, inadequate cardiac output, and inlet cannula obstruction leading to low cardiac output were associated with the inability to wean a patient from mechanical support regardless of the type of support. When these same events were analyzed by device type, pneumatic pulsatile versus centrifugal in relation to the weaning status, only bleeding was significantly different, with this event being more likely to occur and negatively affect weaning in the vortex pump group. Infection was significantly associated with weaning overall, but was only associated with weaning in those patients with pneumatic devices. This is likely on the basis of the two times longer average support times with the pneumatic pulsatile devices versus the centrifugal devices. When these complications were analyzed in those patients

weaned from circulatory support in an attempt to associate such with hospital death or discharge, only renal failure, perioperative myocardial infarction, and infection had a significant negative impact in a univariant fashion regardless of the type of support or the device used. Biventricular failure, however, reached near significance. Although there was no statistical difference in the rates of weaning based on age, there was a significant decrease in hospital discharge in patients older than 70 years. A 13% salvage rate was recorded. Device dependency was seen only in 8% of unweanable patients, and three-quarters of those device-dependent individuals had no immediate contraindications to transplantation. Staged orthotopic heart transplantation was then carried out in 20 of the 32 patients, with 63% ultimately surviving after transplantation. These results are nearly equivalent to those seen in the standard bridge-to-transplantation application.

In conclusion, the available devices appear to provide reasonable and safe circulatory support with equivalent results in the postcardiotomy cardiogenic shock application with both nonpulsatile centrifugal and pulsatile pneumatic devices. Myocardial recovery and acceptable short-term results can be expected in about 25% of patients who otherwise would have been expected to die. Complications during support are frequent, but those limiting patient survival are not exclusively device-related. In fact, some are technical errors in cannula positioning, unrecognized patent foramen, or unrecognized or inadequately treated right ventricular failure. Many are patient-related based on underlying disease, the surgeon's ability to correct myocardial pathology, the patient's physiologic reserve, and the duration of shock, as well as cardiopulmonary bypass time before the institution of circulatory support. Fortunately, pump dependency is rare, but when such occurs, staged transplantation can be carried out in those patients without contraindications to transplantation with reasonable results. However, caution may be advised in instituting circulatory support in patients older than 70 years. As might be expected, physiologic reserve is limited and the final outcome, less than desired. Future studies designed to clearly define those patient selection criteria and the associated variables that might allow for optimal timing of the institution of circulatory support are needed.

Circulatory Support in Conjunction With Cardiac Transplantation

Approximately one-fifth to one-third of all potential cardiac transplant recipients die before a donor organ is located. Furthermore, cardiac complications including inadequate donor organ preservation, acute rejection, and right-sided failure account for a large percentage of the early deaths after transplantation. With these in mind, the database in regard to the use of circulatory support in conjunction with transplantation at present consists of 66 reporting centers. Thirty-two of the centers are in the United States and 34 are outside the continental US. Demographically, there were 544 implants reported with 81% being in male patients with a mean age of 44 years.

Nineteen percent of the implants were in female patients, who were somewhat younger than their male counterparts, averaging 35 years of age. The marked male predominance was likely related to the large number of potential cardiac recipients with ischemic cardiomyopathy. The age distribution for circulatory support in conjunction with heart transplantation obviously parallels that seen in those individuals undergoing isolated cardiac transplantation. However, the best results in terms of the highest percent of patients receiving transplants and then subsequently being discharged occurs at the younger end of the age spectrum, with 80% receiving transplants and 81% of those receiving transplants surviving, and the worst results at the older end of the age spectrum, being a 50-50 proposition. A trend was present. However, the small sample size precluded statistical significance.

The indications for mechanical circulatory support were hemodynamic deterioration before transplantation in 436 patients, acute rejection in 40 patients, and postcardiotomy cardiogenic shock not considered related to acute rejection in 68 patients. In the 40 patients treated with circulatory support during rejection, only 23 (58%) underwent a second transplantation and 8 of the 23 patients (35%) ultimately were discharged from the hospital. This was an absolute salvage rate of about 20%. The 68 patients suffering from posttransplantation cardiogenic shock not related to rejection considered potentially reversible were presented for interest, but were not included in the subsequent analysis because myocardial recovery was anticipated or intended. The weaning rate of 29% was significantly lower than what has been reported in postcardiotomy shock after nontransplant procedures, which is 45% to 50%. However, the probability of being discharged from the hospital after device weaning was about two-thirds, which is a bit higher than the 50% or so reported in other postcardiotomy cardiogenic shock syndromes. Therefore, the absolute salvage rate was about 19%. This was statistically equal to that seen with postcardiotomy cardiogenic shock after other types of procedures.

The duration of circulatory support in these patients was quite variable, and underscores the necessity of the devices used in conjunction with transplantation to provide safe and reliable assistance over a wide range of times (range, 0 to 438 days). There was absolutely no statistical difference in the duration of support based on the type of device, ie, ventricular assist device versus total artificial heart. Interestingly, the experience failed to show that shorter durations of circulatory support are associated with a more favorable outcome. There was no difference statistically between those patients who did not undergo transplantation, the patients who underwent transplantation and died, and those who underwent transplantation and were subsequently discharged from the hospital.

The overall results of circulatory support by device type are depicted in Table 2. Of the 476 patients, 122 received isolated left ventricular support. Approximately 71% of those patients went on to subsequent transplantation, and 87% of those patients were then discharged from the

Table 2. Overall Results of Circulatory Support by Device Type

Device	No. of Patients	Transplanted	Discharged
RVAD	4	1 (25.0%)	1 (100%)
LVAD	122	87 (71.3%)	76 (87.4%) ^a
BVAD	161	105 (65.2%)	73 (69.5%) ^b
TAH	189	135 (71.4%)	67 (49.6%) ^c
Total	476	328 (68.9%)	217 (66.2%)

^{a-c} Fisher's exact two-tailed test: ^a LVAD versus BVAD, $p = 0.003$; ^b BVAD versus TAH, $p = 0.002$; ^c LVAD versus TAH, $p = 0.000$.

BVAD = biventricular assist device; LVAD = left ventricular assist device; RVAD = right ventricular assist device; TAH = total artificial heart.

hospital. One hundred sixty-one of the total patients were managed with biventricular paracorporeal assist devices and 65% of those underwent transplantation. Seventy-three of the 105 patients, or about 70%, were then discharged from the hospital. One hundred eighty-nine patients received pneumatically driven total artificial hearts, 71% underwent transplantation, and nearly 50% of those patients were then discharged from the hospital. The rates of transplantation were statistically equal regardless of the type of support employed. However, if one compared the outcome based on whether a patient received a total artificial heart or a ventricular assist device, there was a highly statistically significant difference with the best outcome seen with univentricular support, then biventricular paracorporeal support, and least favorable with the total artificial heart. The rates of subsequent transplantation, as well as hospital discharge, were identical in patients who received either a pneumatic assist device, an electrically activated device, or a centrifugally driven left ventricular assist device. However, those patients receiving centrifugal devices did fare less well overall, and if the sample size were a bit larger, it is conceivable that there would be statistical significance. The 30-day operative mortality with isolated orthotopic heart transplantation has remained at 10% to 12%. On the other hand, in those patients receiving transplants after device support, the mean operative mortality was about 18%. However, it was 9% for univentricular support, 18% for biventricular support, and 23% for total artificial hearts. The differences were highly significant between the ventricular assist devices and the total artificial heart. However, this did not reach statistical significance between the group of patients with biventricular support and the group with the total artificial heart. Kaplan-Meier survival estimates for all patients undergoing staged cardiac transplantation at 1 and 2 years after the procedures inclusive of the 30-day operative mortality were nearly 65%. This is in contrast to the nearly 80% actuarial survival in an isolated orthotopic cardiac transplant. However, when survival estimates were prepared for each type of mechanical support employed in conjunction with transplantation, the 1- and 2-year estimates for univentricular support were equivalent to isolated orthotopic

Table 3. Complications Precluding Heart Transplantation

Complication	Percentage of Patients (n = 148)
Bleeding	27% ^a
Biventricular failure	27% ^a
Renal failure	33% ^a
Respiratory failure	27% ^a
Infection	24% ^a
Multiorgan failure	15% ^a

^a Univariate predictor of not receiving a subsequent transplant.

cardiac transplantation at about 86% and 83%, respectively. Statistical analysis would bear out highly significant differences, with the best results obtained with univentricular support, then biventricular, and the least favorable with a total artificial heart.

The complications precluding transplantation after establishing circulatory support are listed in Table 3. Many of the patients suffered more than one complication. However, each of the listed complications was a univariate predictor of not receiving a subsequent transplant. Stepwise logistic regression analysis indicated in decreasing order of importance that bleeding, neurologic events, and biventricular and renal failure had a significant negative effect on future transplantation. The causes of 30-day mortality in these patients after staged transplantation indicated any patient may have had more than one factor. Univariate analysis indicated that bleeding, renal

failure, persistent respiratory failure, infection, and rejection negatively affected hospital discharge. Multivariate analysis indicated that bleeding, infection, and renal failure were the most important predictors of hospital death after staged transplantation. The causes of death after 30 days parallel those of the general isolated cardiac transplant population.

In conclusion, it would seem these results in the bridge-to-transplantation application are quite encouraging where support is instituted for hemodynamic instability and immediate donor organ unavailability. Nearly three-quarters of the patients will undergo subsequent transplantation when the initial support is univentricular and with an electric or pulsatile pneumatic device. Furthermore, in patients who receive transplants 30-day mortality and long-term survival are nearly equivalent to those in patients having isolated orthotopic cardiac transplantation. Certainly, we will continue to learn many important patient and device selection lessons, and only ongoing, careful clinical trials will improve the rates of successful transplantation. Ideally, it would be advantageous to be able to prospectively identify those patients requiring only univentricular support. It is likely that this information derived from staged cardiac transplantation will also have an impact on the future clinical trials slated for chronic totally implanted devices.

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Current Expectations in Dynamic Cardiomyoplasty

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Dynamic cardiomyoplasty has been evaluated in the treatment of severe cardiomyopathies. This report outlines the results of this procedure in 21 patients with dilated or ischemic cardiomyopathy who were in New York Heart Association class III or IV before operation. There were no operative deaths. Patients were followed up for a mean of 17.6 months. Eight patients died during late follow-up, and actuarial survival rates were 73.2% at 1 year and 65.9% at 2 years of follow-up. Functional class improvement was documented in the surviving patients. Furthermore, significant improvement in left ventricular

function was demonstrated by radioisotopic angiography and by heart catheterization for more than 2 years after the operation. These studies documented that left ventricular ejection fraction increased as a result of global improvement in regional wall motion. Absence of clinical and hemodynamic improvement after cardiomyoplasty seems to be related to muscle flap ischemic compromise, whereas the patient's condition before operation seems to influence the long-term outcome of cardiomyoplasty.

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Dynamic cardiomyoplasty has evolved rapidly in the last 6 years. After the pioneering efforts of the Broussais Hospital group, in Paris, this surgical procedure has been evaluated throughout Europe, South America, Canada, and the United States. It has been indicated to partially replace or reinforce the heart muscle in the treatment of left ventricular (LV) tumors or aneurysms [1-6] and in patients with severe cardiomyopathies [2, 4-9].

Initial outcomes demonstrated the improvement of LV function and reversion of congestive heart failure in patients with dilated cardiomyopathies after cardiomyoplasty [8, 9]. This technique has also been reported in a heterogeneous group of patients and associated with other procedures [1-6] and devices that provide different muscle stimulation [6, 7], making difficult the analysis of cardiomyoplasty benefits.

The purpose of this report is to outline the results of dynamic cardiomyoplasty in the treatment of patients with advanced heart failure due to dilated or ischemic cardiomyopathy at the Heart Institute of São Paulo University Medical School. Present trends in this field will also be reviewed.

Patients and Methods

Patient Selection

Patients currently selected for cardiomyoplasty are those at high risk of dying within 1 year due to severe cardiomyopathies, which does not essentially differ from heart transplantation criteria [10]. Nevertheless, these patients need to be stable enough on medical therapy to withstand a waiting period of 6 to 8 weeks before effective skeletal

muscle flap adaptation. Serious mitral regurgitation, medically untreated arrhythmias, and major enlargement of the left ventricle are also considered contraindications to this procedure.

Dynamic cardiomyoplasty was performed in 21 patients at our institution between May 1988 and September 1991. Fifteen patients were in New York Heart Association (NYHA) class III and 6 were in class IV despite the use of maximal conventional medical therapy. The cause of heart failure was idiopathic dilated cardiomyopathy in 17, Chagas' disease cardiomyopathy in 2, and ischemic cardiomyopathy in 2 patients. Patients' ages ranged from 16 to 57 years (mean, 43.2 years), and 18 patients were male. Preoperative laboratory data are summarized in Table 1. Three patients had chronic atrial fibrillation and 10 had nonsustained ventricular tachycardia episodes documented by Holter recordings. Cardiac catheterization showed compromise of coronary arteries in 2 patients, mild mitral insufficiency in 11, and moderate mitral insufficiency in 4. Standard spirometric study documented mild restrictive compromise of the ventilatory function in 16 patients. All patients signed a special informed consent under the Scientific Committee of the Heart Institute of São Paulo University Medical School.

Surgical Procedure

Dynamic cardiomyoplasty was performed by means of two separate incisions: a lateral approach for muscle flap dissection and a median sternotomy for cardiac access. Dissection and transposition of left latissimus dorsi muscle followed the technique described by Chachques, Grandjean, and Carpentier [11]. The muscle flap was wrapped around the ventricular surfaces as previously described [8, 9], providing a left posterior cardiocostal wrapping [12]. Two intramuscular pacing electrodes (Medtronic SP 5528, Maastricht, the Netherlands) were implanted in the skeletal muscle graft, and an epimyocar-

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Table 1. Preoperative Laboratory Data^a

Variable	Value
Thorax roentgenogram	
Cardiothoracic ratio	0.58 ± 0.03
Doppler echocardiography	
LV diastolic diameter (mm)	73.4 ± 7.8
LV segmental wall shortening (%)	11.6 ± 2.2
Radioisotopic angiography	
LV ejection fraction	0.20 ± 0.04
RV ejection fraction	0.23 ± 0.06
Right heart catheterization	
Cardiac index (L/min · m ²)	1.72 ± 0.23
Pulmonary wedge pressure (mm Hg)	25.8 ± 5.6
Cardiopulmonary exercise test	
Maximum oxygen consumption (mL · kg ⁻¹ · min ⁻¹)	15.4 ± 4.1

^a Values are shown as mean ± standard deviation.

LV = left ventricular; RV = right ventricular.

dial sensing lead (Medtronic SP 5548) was placed in either the right or left ventricle. The Medtronic SP 1005 cardiomyostimulator was used for muscle flap stimulation. Further, 1 patient with ischemic cardiomyopathy underwent saphenous vein aortocoronary bypass grafting into the right coronary artery without cardiopulmonary bypass.

Electrical stimulation of skeletal muscle flap started 2 weeks after the operation, and a progressive muscle conditioning protocol was followed [13]. At the late postoperative period, muscle flap was paced in 1:1 mode with the heart rate. Pulse train stimulation was used with a burst frequency of 30 Hz and associated with supramaximal pulse amplitude values to avoid ineffective muscle flap contraction. The delay between the ventricular sensed event and the muscle burst was adjusted to provide an exact synchronization between muscle flap contraction and ventricular systole [8].

Follow-up Protocol

Patients were studied every 6 months after the operation by means of Doppler echocardiography, radioisotopic angiography, right heart catheterization, 24-hour Holter recordings, and cardiopulmonary exercise test, as previously published [8, 9].

Left ventricular catheterization was performed after 1 year of follow-up with the cardiomyostimulator on and turned off for at least 24 hours. Cineangiograms were recorded at right anterior oblique view. End-diastolic and end-systolic endocardial contours were analyzed by means of computer software. Left ventricular ejection fraction was calculated by the area-length method [14], and regional wall motion was quantified using the center line method [15].

Statistical Analysis

One-way analysis of variance and paired Student's *t* test were used to compare data before and after cardiomyo-

plasty and data obtained with the cardiomyostimulator turned on and off. Cumulative mortality rates over time were determined by the actuarial method, and differences between them were assessed by the log-rank test. A value of *p* less than 0.05 was considered significant. Laboratory data are presented as mean ± standard deviation, whereas survival rates are presented as mean ± standard error of the mean.

Results

Immediate Surgical Results

There were no operative deaths in this series. Dopamine or dobutamine and sodium nitroprusside were prophylactically used to maintain normal cardiac output during cardiomyoplasty and the first week after the operation.

Immediate postoperative course was in general uneventful. A transient period of multiple organ failure developed in 2 patients, 2 patients had atrial fibrillation or flutter, and 1 patient had pulmonary infection. In addition, left arm paresis was observed in 2 patients for 2 months after cardiomyoplasty.

Muscle flap ischemic compromise was monitored by variations in the serum level of creatine kinase, which showed a mean peak value of 984 ± 568 IU at 38 ± 18 hours of follow-up. Four patients had peak values of creatine kinase greater than 1,500 IU, among them the 2 patients in whom transitory multiple organ failure developed. One of these patients had absence of muscle flap contraction with maximal electrical stimulation and died of congestive heart failure 2 months after the operation. Latissimus dorsi normal fibers intermingled with areas of fibrosis were documented by microscopic study. Poor muscle flap contraction was observed under pulse train stimulation in the remaining 3 patients.

Eighteen patients completed the muscle conditioning protocol and were followed up from 4 to 41 months (mean, 20.1 ± 11.5 months). One patient remains in the muscle conditioning period and 1 patient died at 2 months of follow-up owing to severe pulmonary thromboembolism and infection.

Circulatory Function Evaluation

At 6 months of follow-up, radioisotopic angiography demonstrated that LV ejection fraction improved from 0.21 ± 0.04 to 0.25 ± 0.07 (*p* = 0.01). However, this variable did not change in the 3 patients with significant increases in creatine kinase level at the immediate postoperative period and in 1 patient with an LV internal diastolic diameter of 89 mm. There was no variation in right ventricular ejection fraction after the cardiomyoplasty (0.24 ± 0.06 versus 0.25 ± 0.07).

Left ventricular cineangiographic study, performed in 10 patients at 16 ± 4 months of follow-up, documented that ejection fraction increased in patients who survived long-term after cardiomyoplasty from 0.15 ± 0.08 to 0.31 ± 0.08 (*p* = 0.01). This improvement resulted from a global modification of LV wall motion as depicted in Figure 1. This study also showed a decrease in LV ejection

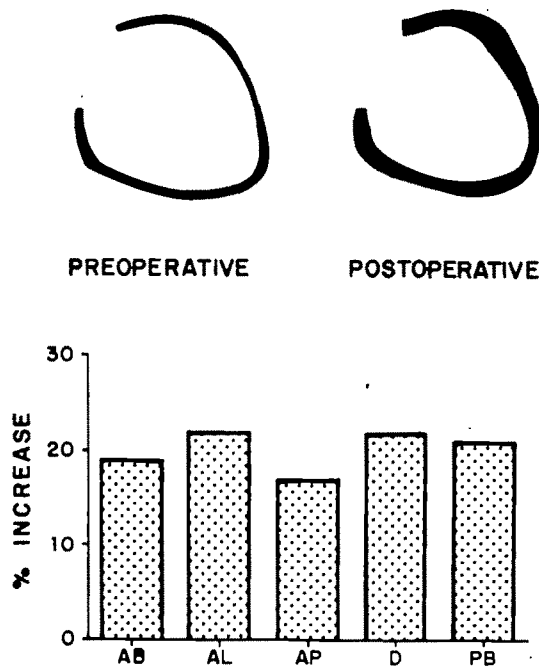


Fig 1. Left ventricular regional wall motion, obtained by end-diastolic and end-systolic contour traces, before and after dynamic cardiomyoplasty. The bar graph shows the percent increase in this variable in the anterobasal (AB), anterolateral (AL), apical (AP), diaphragmatic (D), and posterobasal (PB) regions in the postoperative period.

fraction to 0.23 ± 0.13 when the cardiomyostimulator was turned off for 24 hours ($p = 0.06$).

Right heart catheterization demonstrated that cardiac index increased from 1.76 ± 0.28 to 1.93 ± 0.3 L/min $\cdot$ m ^{2} at 6 months of follow-up ($p = 0.04$) and showed a significant improvement in global circulatory function, as documented by LV stroke work index and pulmonary wedge pressure variations (Fig 2). This hemodynamic improvement and LV ejection fraction increase persisted for 12 and 24 months after the cardiomyoplasty, as shown in Table 2.

Survival and Quality of Life

Six of the 18 patients who completed the muscle conditioning period and were followed up long-term died;

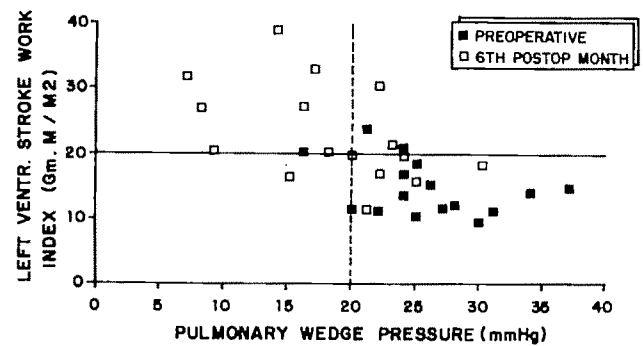


Fig 2. Left ventricular stroke work index and pulmonary wedge pressure variations from the preoperative period to the sixth month of cardiomyoplasty follow-up.

actuarial survival rates are depicted in Figure 3. The causes of death were progression of heart failure associated with pulmonary infection, cerebral vascular accident, or renal failure in 3 patients; pulmonary thromboembolism in 1 patient; and sudden death in 2 patients who died after the second year of follow-up. Progression of heart failure occurred in patients without postoperative improvement of LV function, whereas patients who died suddenly were under medical therapy for severe tachyarrhythmias.

Furthermore, patients operated on in NYHA class III had a survival rate of 86.1% at 1 year and at 2 years of follow-up, whereas actuarial survival rates for patients operated on in NYHA class IV were 50% and 33.3% at the same periods ($p = 0.02$).

Among the 12 surviving patients in long-term follow-up, 6 returned to NYHA class I, 5 are in class II, and 1 is in class III, some of them using fewer drugs or lower doses than they did in the preoperative period. Nine of these patients resumed their professional activities.

Comment

Improvement of LV function with dynamic cardiomyoplasty is documented in patients with dilated or ischemic cardiomyopathies. In these patients, LV ejection fraction increases as result of global improvement in regional wall

Table 2. Sequential Hemodynamic and Radioisotopic Data^a

Variable	Preoperative	Follow-up			p Value
		6 months	12 months	24 months	
LVEF	0.21 ± 0.04	0.25 ± 0.07	0.27 ± 0.09	0.27 ± 0.04	0.01
RVEF	0.24 ± 0.06	0.25 ± 0.07	0.28 ± 0.09	0.28 ± 0.05	NS
CI (L/min $\cdot$ m ^{2})	1.76 ± 0.28	1.93 ± 0.29	1.92 ± 0.38	1.93 ± 0.3	0.06
SI (mL/m ^{2})	18.5 ± 2.5	23.5 ± 5.6	24.5 ± 6.4	23.7 ± 5.5	0.01
RAP (mm Hg)	8.2 ± 3.5	7.2 ± 3.8	7.5 ± 4.7	8.3 ± 2.3	NS
PAP (mm Hg)	37.2 ± 8.3	28.5 ± 10	25.8 ± 11.4	23.9 ± 9.6	0.01
PWP (mm Hg)	25.5 ± 5.5	18.5 ± 6.3	17.8 ± 5.3	16.6 ± 5.9	0.01
AoP (mm Hg)	83.7 ± 9.2	90.9 ± 8.8	90 ± 8.8	96.2 ± 5.4	0.01

^a Values are shown as mean $\pm$ standard deviation.

AoP = aortic pressure; CI = cardiac index; LVEF = left ventricular ejection fraction; NS = not significant; PAP = pulmonary artery pressure; PWP = pulmonary wedge pressure; RAP = right atrial pressure; RVEF = right ventricular ejection fraction; SI = stroke index.

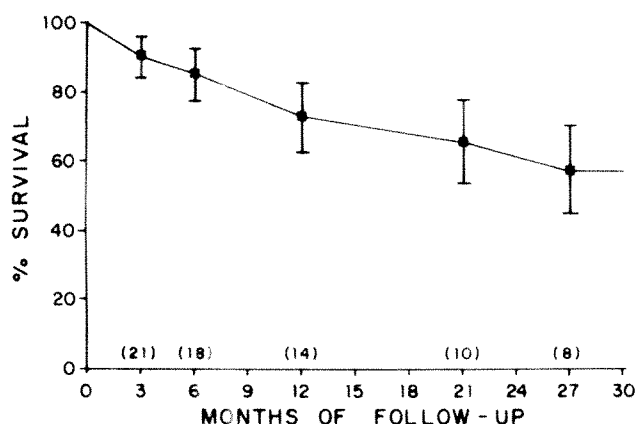


Fig 3. Plots of actuarial survival rates after dynamic cardiomyoplasty. Numbers in parentheses indicate patients followed up in the preceding period. Values are shown as mean $\pm$ standard error of the mean.

motion, and the mechanism of action seems to be essentially the augmentation of systolic function through the action of synchronized skeletal muscle contraction. This mechanism has been widely demonstrated in experimental reports [13, 16-19]. Furthermore, this concept was confirmed to some extent by the LV ejection fraction decrease when the cardiomyostimulator was turned off in the late follow-up period in this study.

Although LV ejection fraction increase and cardiac output augmentation at rest seems to be modest in patients with severe cardiomyopathies, cardiomyoplasty's impact on circulatory function may be better evaluated by its significant influence on LV stroke work and pulmonary pressures. In addition, more evident changes in cardiac output and global circulatory function have been clinically documented, especially during exercise [20].

Besides these hemodynamic benefits, dynamic cardiomyoplasty may also influence the mechanical properties of the failing heart itself. Reduction in LV wall stress was demonstrated after this surgical procedure in a canine model of dilated cardiomyopathy [19], indicating that cardiomyoplasty may decrease myocardial oxygen consumption as previously suggested [9]. Accordingly, in a dilated, failing left ventricle, the afterload matching and the myocardial contractility may be partially restored and slow progression of the underlying cardiomyopathy may result from this mechanism [21]. The maintenance of LV ejection fraction and hemodynamic improvement for more than 2 years after the operation in the present report indicates that this may occur clinically. Also, cardiomyoplasty's influence on LV diastolic compromise was documented by Doppler echocardiography, indicating partial recovery of myocardial compliance at late follow-up [22].

Cardiomyoplasty benefits may be influenced by technical aspects and by skeletal muscle flap response to electrical stimulation. Better LV ejection fraction improvement has been documented in patients with lesser LV end-diastolic dimensions, which is in general agreement with Laplace's law [8]. Furthermore, absence of LV ejec-

tion fraction increment occurred in patients with important muscle flap ischemic compromise after the operation. This event demonstrates the importance of skeletal muscle contractile state for cardiomyoplasty effectiveness and shows the necessity to preserve normal muscle flap perfusion in the immediate postoperative period. The optimal orientation of muscle fiber direction [18], the extent of the wrap around the heart [22], and the optimal stimulation protocols for transformation and assist [8, 13] remain controversial.

Improvement in functional class and exercise capacity has been demonstrated by overall clinical experience with dynamic cardiomyoplasty [2-4, 6, 7, 23]. In addition, cardiomyoplasty's influence on the survival of patients with advanced heart failure has been suggested by several authors [2, 4, 9, 23].

Reversion of congestive heart failure and a significant increase in maximal oxygen consumption during treadmill test were documented by our group for at least 2 years after cardiomyoplasty in patients with dilated cardiomyopathies [22, 23]. Furthermore, this surgical procedure may be performed in these patients with low operative mortality. Long-term survival improvement with cardiomyoplasty was also demonstrated in patients with dilated cardiomyopathies, comparing cardiomyoplasty results with the natural history of this disease under medical therapy [23]. Patients operated in functional class IV, however, exhibited a significantly higher mortality than those operated on in class III, suggesting that the patient's condition before the operation plays an important role in the long-term outcome.

Progression of heart failure was an important cause of death after cardiomyoplasty in patients with severe cardiomyopathies. Nevertheless, it was related to patient selection criteria or to technical limitations, which may be improved. There were also deaths caused by pulmonary thromboembolism and deaths that occurred suddenly in patients with documented tachyarrhythmias. These complications are probably not affected by cardiomyoplasty itself. However, they frequently occur in patients with advanced heart failure and still need effective means to be precluded [24]. The deleterious effects of ventricular arrhythmias on cardiomyoplasty results were also reported by other authors [7, 25]. Furthermore, active myocarditis [26] and right ventricular function compromise in patients with ischemic cardiomyopathy [6] have also been related to cardiomyoplasty mortality.

Interpretation of the current clinical experience with dynamic cardiomyoplasty is limited. This surgical procedure improves LV function, reverses congestive heart failure, and seems to improve long-term survival of patients with severe cardiomyopathies. Nevertheless, the improvement of LV function with cardiomyoplasty may be limited by technical aspects and by the possibility of muscle flap damage. Also, cardiomyopathy's steady evolution after cardiomyoplasty may be influenced by the patient's condition before operation, suggesting that this procedure should be better indicated in patients with mild or moderate heart failure.

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Emergency Resuscitation Using Portable Extracorporeal Membrane Oxygenation

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Manual cardiopulmonary resuscitation is currently the standard treatment for cardiac arrest patients both in and out of the hospital. Accumulated experimental and anecdotal clinical evidence suggests enhanced survival in patients with extreme circulatory decompensation who have been emergently supported with portable cardiopulmonary bypass. Long-term survival is possible even when application is delayed, but early institution of support after cardiac arrest in selected patients offers the best survival advantages. In our hospital this has been achieved by training a team of in-house personnel to

emergently prepare, apply, and temporarily manage cardiopulmonary bypass until personnel with greater specialty training arrive. Machinery needed to perform emergency cardiopulmonary bypass is currently available in all hospitals with open heart surgery programs. Simple support is often therapeutic but can also serve as a bridge to definitive diagnostic and other therapeutic procedures. Commercial units are becoming more biocompatible and easier to use, making both wider application and more prolonged support likely in the future.

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The first reported experience with closed chest methods of augmenting circulation was by Boehm in 1878 [1], working with arrested cats. It was not until 1947 that Gurvich and Yuniev [2] were able to effectively cardiovert experimentally induced ventricular fibrillation. They found that cardioversion was not possible if arrest lasted more than 1.5 minutes. However, this interval could be extended to 8 minutes if external compressions of the chest were used. Working on this background, Kouwenhoven and associates [3] described the technique of applying their alternating current defibrillator to patients undergoing closed chest cardiopulmonary resuscitation (CPR) in 1960. Cardiopulmonary resuscitation has subsequently become standard therapy for cardiac arrest patients, whether in or out of the hospital.

The physiology of extreme circulatory decompensation has been evaluated both experimentally and clinically [4, 5]. During cardiac arrest with closed chest massage, cardiac output falls to approximately 20% of normal. Systolic arterial pressure is maintained, but mean arterial pressure falls below the average level of approximately 60 mm Hg because of low diastolic pressures. Venous pressure gradually rises above the normal level of 5 mm Hg to as high as 20 to 30 mm Hg. Rising venous pressure and falling mean arterial pressure gradually create an inadequate peripheral tissue perfusion gradient, which, coupled with low cardiac output, results in multi-

ple organ failure. Because of the cumulative nature of injuries incurred during CPR, it is not surprising that during experimental or clinical cardiac arrest, survival is extremely rare if CPR lasts longer than 30 minutes [6, 7].

Abnormal circulatory dynamics can be rapidly corrected by the peripheral application of venoarterial bypass using an oxygenator. During cardiopulmonary bypass, the central venous pressure falls to desirably low levels as mean arterial pressure and cardiac output rise. As seen in Figure 1, application of peripheral bypass establishes the circulatory milieu necessary for peripheral organ sustenance and maintenance. In the detailed work of Levine and colleagues [7], advantages of peripherally applied cardiopulmonary bypass for resuscitating animals following cardiac arrest was demonstrated. The results are summarized in Figure 2. After 30 minutes of cardiac arrest with standard cardiopulmonary resuscitation, a control group of animals was subjected to advanced life support, which included the application of cardiostimulant drugs. The test group was placed on peripheral cardiopulmonary support. All animals receiving peripheral cardiopulmonary support versus 50% of the animals on advanced life support were easily cardioverted. At 24 hours, 7 of 10 animals on peripheral cardiopulmonary support survived with normal central nervous system function compared with 3 of 10 animals receiving advanced life support, 2 of which had normal cerebral function. Thus it appears that application of cardiopulmonary bypass to arrested animals, even after 30 minutes of CPR, can result in improved survival as compared with CPR with advanced life support alone. Clinical experiences suggest that the same is true in humans [8-11].

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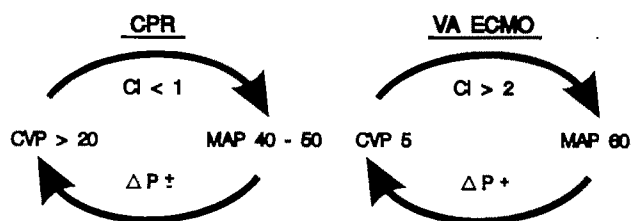


Fig 1. The hemodynamics produced during cardiopulmonary resuscitation (CPR) are summarized on the left. The cardiac index (CI) is usually less than $1 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$. The central venous pressure (CVP) rises as the mean arterial pressure (MAP) falls. This produces a marginal tissue perfusion gradient (ΔP). Introduction of peripherally applied venoarterial (VA) extracorporeal membrane oxygenation (ECMO) immediately creates a satisfactory cardiac index and improves the peripheral tissue perfusion gradient.

Technology Available for Portable Extracorporeal Membrane Oxygenation

Following the work of Stephen Phillips and co-workers [12], a variety of companies (Bard Cardiopulmonary Division, Tewksbury, MA; Sarns 3M Health Care, Ann Arbor, MI; Medtronic, Inc, Minneapolis, MN) have developed commercially available portable cardiopulmonary bypass systems that can be percutaneously applied. All are relatively simple to prime and, in fact, some experimental work has now been done with systems that remain permanently primed. The most encouraging recent development has been the clinical use of heparin-coated peripheral bypass circuits. These coated surfaces offer two advantages. First, they are minimally thrombogenic, and second, they are known to diminish the activation of blood components contacting them. The diminished activation of the complement cascade, preserved platelet

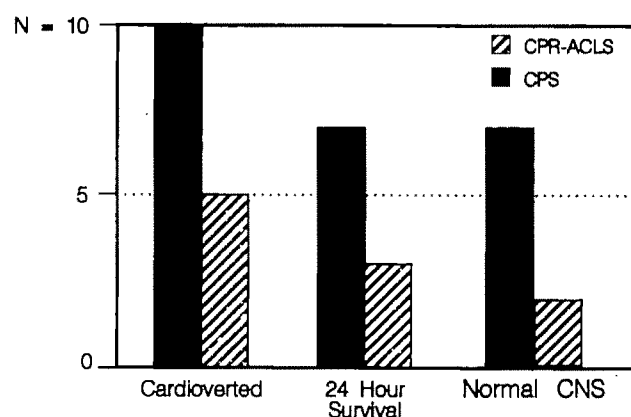


Fig 2. Experimental evidence demonstrating improved survival after 30 minutes of cardiac arrest with cardiopulmonary resuscitation in animals supported by peripherally applied extracorporeal membrane oxygenation and venoarterial bypass (CPS) when compared with animals receiving continued cardiopulmonary resuscitation with the addition of advanced cardiac life support technique (CPR-ACLS). (CNS = central nervous system.) (Reprinted from Levine R, Gorayeb M, Safar P, Abramson N, Stezoski W, Kelsey S. Cardiopulmonary bypass after cardiac arrest and prolonged closed-chest CPR in dogs. *Ann Emerg Med* 1987;116:620-7, by permission.)

levels, normal patient prothrombin time, partial thromboplastin time, and bleeding times associated with the use of these circuits have permitted their application in situations where hemorrhage is either an active or a potentially active problem. They have successfully supported patients with multiple trauma and patients requiring major operations. An unproven possible advantage of using coated circuits for emergency cardiopulmonary bypass, where the usual precoating of a circuit with albumin is impractical, is that the more biocompatible surfaces may reduce the incidence of multiple systems injury in emergently supported patients with shock.

Surgical Techniques

Venous Cannulation

Because the portable systems do not use a reservoir and therefore aspirate blood directly from the heart, higher flows through relatively small-bore cannulas can be achieved. This is in contrast to conventional cardiopulmonary bypass, where relatively large-bore venous cannulas are used in a gravity drainage system to fill a reservoir. Twenty French venous cannulas can be percutaneously positioned in the right atrium, either through the femoral vein or through the right internal jugular vein. In our own experience, emergency percutaneous femoral cannulation has occasionally resulted in retroperitoneal venous disruption requiring circulatory arrest for the repair and ultimate survival of 1 patient. Retroperitoneal perforation can be averted by the use of internal jugular vein as a percutaneous right atrial access site. Repair is simpler in the rare patient with internal jugular vein injury. Furthermore, venous flows are apt to be higher because of the shorter catheters required for more certain direct right atrial access.

Arterial Cannulation

Arterial blood is returned to the femoral artery. Because patients in cardiac arrest generally suffer the arrest because of cardiac dysfunction, not pulmonary dysfunction, it is not necessary to direct the arterial blood flow back to the supravalvular region. The cannulas can be placed percutaneously using a Seldinger technique with progressive dilation of the artery or, especially in arrested patients, by cut-down usually combined with the modified Seldinger technique. Rapid peripheral arterial access may not be possible in patients with aortoiliac occlusive disease. Even when cannulated, obstructive disease in some patients does not permit adequate retrograde perfusion. In occasional patients the small, high-flow jet from the arterial cannula can dislodge atheromatous excrescences and produce systemic arterial embolization. Rarely peripheral cannulation can result in aortic dissection. In patients in whom prolonged perfusion is required, it may occasionally be necessary to cannulate the peripheral femoral artery and vein to prevent leg ischemia and venous stasis.

Oxygenators

The oxygenators that are currently most commonly used for emergency cardiopulmonary bypass are those using

"hollow fiber" membranes. Because the fibers are not true membranes but are microporous, they tend to progressively exude plasma after 12 to 36 hours of use. In the future, diminishing pore size as well as the potential addition of silicone coat to one side of the fiber will eliminate plasma leakage. Available oxygenators with heparin-coated fibers are minimally thrombogenic; however, all are currently constructed in biologically improbable ways, which create thrombosis in areas of stasis. This problem makes the use of some circulating heparin desirable.

Pumps

Two types of pumps are used in emergency cardiopulmonary resuscitation with portable bypass units. The most widely applied types are the nonocclusive, pressure-limited centrifugal pumps. Currently, the most frequently used is the Bio-Medicus pump, followed by the Sarns pump and then the St. Jude pump. All three are minimally hemolytic, although over long-term use, they appear to be mildly thrombogenic. The advantage that they offer for emergency cardiopulmonary bypass is that the centrifugal pumps are pressure-limited and, therefore, any abrupt occlusions of inflow and outflow cannulas are unlikely to result in either aspiration of air or disruption of lines. Their use in long-term support is less desirable because of their thrombogenicity.

The second type of pump that can be used for peripheral resuscitating bypass units is the common roller pump. These pumps are not pressure-limited and consequently can develop extremely high venous inflow and arterial outflow pressures. This can make emergency use of these pumps somewhat cumbersome if patient mobility is important. For support lasting more than 1 or 2 days, these pumps become more advantageous.

Conduct of Emergency Cardiopulmonary Bypass

After vascular access has been established, cardiopulmonary bypass is begun and conducted in the usual way with a few exceptions. Because peripherally applied cardiopulmonary bypass usually does not capture all venous return to the heart, some blood may continue to flow through the lungs, into the left ventricle, and, subsequently, to the coronary arteries and cerebral circulation. Thus, continued high endotracheal oxygen insufflation is necessary to prevent desaturated blood from being ejected from the left ventricle. Distention resulting from varying amounts of aortic insufficiency and bronchial flow filling the arrested left heart can be minimized by prompt defibrillation of the heart. Cardioversion is made easier by collapsing the engorged left ventricle using simple sternal compression. Experimental left ventricular decompression during peripheral cardiopulmonary bypass in animals with ventricular fibrillation has been achieved by placing a helical coil across the pulmonary valve to render it incompetent and permit left ventricular decompression [13]. Clinical use of this technique had not been reported. In our own experience, the actual occurrence of left ventricular distention has been minimal. It can be monitored using transthoracic or transesophageal echocardiog-

raphy, or with a pulmonary artery pressure monitoring catheter (pulmonary artery pressure during ventricular fibrillation is equal to the left intraventricular pressure). After the initiation of full cardiopulmonary bypass, arrested patients may suddenly awaken and become combative and require immediate sedation or muscle paralysis.

Because emergency cardiopulmonary bypass is often established in patients who are not fully monitored, the adequacy of perfusion must initially be determined by clinical examination. Temperature of the upper extremities is assessed. The arterial pressure is determined initially using a Doppler apparatus with pressure cuffs and later using arterial monitoring lines. The arterial and venous cardiopulmonary bypass access lines are examined to roughly determine the arterial-venous oxygen difference. If both arterial and venous catheters are desaturated, blood flow to the oxygenator is insufficient. If both are fully saturated, venovenous bypass must be ruled out. Alternatively, in some patients after cardiac arrest with prolonged CPR, peripheral oxygen extraction may be so low that the arteriovenous oxygen difference, even with low flows, is minimal. This usually denotes peripheral organ death and a poor prognosis.

During cardiopulmonary bypass in patients with cardiac arrest due to acute coronary occlusion, it is theoretically advantageous to reduce the systemic temperature to prolong the "safe" ischemic time for the injured heart. Some commercially available emergency cardiopulmonary bypass units have cooling as well as heating units incorporated into their circuits.

Current Results of Clinical Trials Using Portable Emergency Cardiopulmonary Bypass Systems

On the 31st anniversary of the discovery and clinical application of CPR [14], reported results have been less encouraging than the initial experience seemed to project. In two recent reviews of the literature, the current results of CPR on in-hospital patients have been reviewed [6, 15-17]. Approximately 50% of the patients can be resuscitated initially, but only 10% of the patients ultimately leave the hospital. In our experience at Sharp Memorial Hospital in San Diego, the discharge rate had been somewhat higher. Over a 1-year period, approximately 65% (91/140) of 140 arrested patients were resuscitated. Twenty-six percent (23/91) of those patients were discharged. The average duration of CPR was approximately 22 minutes. Many have questioned how widely CPR should actually be applied in the hospital setting. The procedure is expensive, and in those with little hope of long-term survival, it may be inhumane and even undesirable. Each institution must address the patient selection issues individually. Our results of in-hospital CPR have improved primarily by the more judicious application of the technique.

Based on the experimental evidence available, one would expect enhanced survival in patients if, after CPR, they were supported early by judiciously applied peripheral extracorporeal bypass circuits. Control studies evalu-

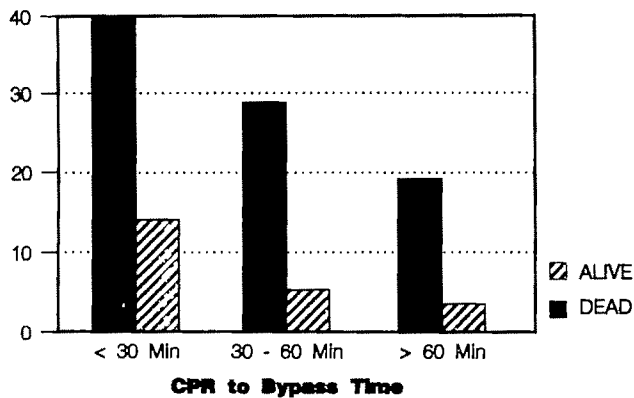


Fig 3. Summary of 1991 Registry data on 116 patients with witnessed arrests. Even with cardiopulmonary resuscitation (CPR) lasting more than 30 minutes, prolonged survival is possible.

ating the technique are unlikely to be created in the near future. The only evidence available is the anecdotal clinical reports now appearing in the literature. Data from the 1991 National Cardiopulmonary Support Registry for emergency applications have been recently reported [18]. The Registry collected information from 17 different institutions treating 187 patients using emergency cardiopulmonary bypass. Forty of 187 patients ultimately survived, for an overall survival rate of 21%. Of the 187 patients, 75% (140/187) had diagnostic and therapeutic interventions performed while on cardiopulmonary bypass. These procedures included pulmonary embolectomy, pulmonary artery bypass grafting, and pulmonary and arterial angiography, as well as angioplasty. When one compares the survivors with the nonsurvivors, approximately 77% (31/40) of the survivors had a therapeutic intervention while being supported, whereas only half (73/147) of the nonsurvivors did. This suggests that the application of cardiopulmonary bypass allows the patient to be transferred to more advanced forms of diagnostic and therapeutic intervention, which might enhance his or her survival. In Figure 3, the results of witnessed arrests in 116 patients reported in the Registry are seen. Although differences between the three groups of arrest times depicted are not statistically significant, it is clear that survival, even after 221 minutes of cardiac arrest, is possible using peripherally applied ECMO.

Because the Registry data represent the broad application of a technology in multiple institutions, some insight can be gained by looking at single-institution experiences. At the 37th Annual Meeting of the American Society for Artificial Internal Organs, Dr Charles Moore [19] reported experience with 67 patients with a 30-day survival rate of 31%. Dr Mooney and associates [8] reported a 64% survival in 11 patients (7/11) undergoing emergency cardiopulmonary bypass. When we analyzed data from our initial reported series and divided the patients into early and late experience, the long-term survival of our most recent cohort was approximately 30% (7/20), compared with the early long-term survival of only 10% (2/20). Our improved survival is the result of better patient selection

as well as an emphasis on early institution of emergency ECMO.

We have created an emergency ECMO team that comprises informed physicians, nurses, and perfusionists. The training for the team includes an initial didactic session describing the physiology of the technology as it is applied to the patient, as well as the potential complications of the devices. Direct, hands-on, "wet lab" experience is also provided during the initial training session. After the introductory training, designated nurses in the hospital carry beepers. They are readily available to bring resuscitative units to the bedside of arrested patients, prime the pump, and begin cardiopulmonary bypass. These nurses participate in laboratory training every 2 months and are able to prime the pump and commence cardiopulmonary bypass within 10 minutes of notification.

Careful attention must be paid to the hospital deployment plan for the use of this potentially lifesaving technology. This must be begun at the bedside by the physician attending the arrested patient. The physician must decide almost immediately if the arrested patient is a good long-term survival candidate. Once that decision has been made, a call for the cardiopulmonary bypass unit, which he or she may or may not ultimately use, is issued. In our hospital, perfusionist and cardiothoracic surgeon are notified as soon as the nurse who brings the unit to the bedside is notified. Cannulas are placed at the bedside by the physician in attendance. Physicians who are capable of percutaneously placing catheters for use as dialysis access conduits in patients are also capable of placing cannulas for extracorporeal circulation. In precarious patients, it is prudent to place percutaneous access lines in the femoral artery, internal jugular vein, or common femoral vein before cardiac arrest. This facilitates the later application of larger bore cannulas after cardiopulmonary arrest, when finding an arterial pulse can be difficult. Cannulas are placed, and the patient is attached to the perfusion unit, which is activated by the nurses. The patient is supported, and the ultimate disposition is decided by the physician in attendance.

Complications

Complications unique to emergency peripherally applied cardiopulmonary bypass are largely related to the emergency vascular access sites. In our reported experience [9], vascular access was not possible in approximately 10% of patients (2/38). In Dr Moore's experience 2 of 53 patients could not be cannulated (as reported at the 37th Annual Meeting of the American Society for Artificial Internal Organs). In the multiinstitutional experience, 26 of 187 patients (14%) experienced technical problems with cannulations, which are summarized in Table 1. For the 135 patients who died, the major organ dysfunctions contributing to death are seen in Table 2. It is not possible to determine whether these maladies were antecedent to or the result of emergency cardiopulmonary bypass. Probably some resulted from delayed institution of cardiopulmonary bypass after prolonged CPR. It is possible that the

Table 1. Complications Related to Bypass

Complication	No. of Patients	Percent
None	161	86.1
Technical perfusion problem—cannulas	6	3.2
Poor venous drainage	5	2.7
Bleeding at groin	2	1.1
Technical perfusion problem—circuit	2	1.1
Arterial injury	1	0.5
Equipment failure	1	0.5
Perforated vena cava	1	0.5
Other	2	1.1
Unknown	7	3.7

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introduction of emergency hemodilutional cardiopulmonary bypass into patients undergoing prolonged CPR may in some way predispose these patients to multiple organ failure syndrome. The Elective Supported Angioplasty Register reported its multiinstitutional experience with the first 100 patients undergoing supported angioplasty. This experience represents a best-case scenario for the introduction of peripheral percutaneous cardiopulmonary bypass in the relatively controlled environment of the cardiac catheterization laboratory [20]. The reported morbidity is seen in Table 3. Understandably, local cannulation problems are less frequent and multisystem organ failure does not appear. A few cases that may be the result of retrograde embolization (cerebrovascular accident, renal failure, small bowel infarction) do appear and may reflect the incidence of this problem in a large population of patients likely to be the recipients of emergency resuscitative cardiopulmonary bypass.

Conclusion

It appears that early, judicious application of emergency cardiopulmonary bypass to properly selected patients in cardiac arrest offers a survival advantage. The devices should be used only in patients with witnessed arrests, with the possible exception of arrested victims suffering from hypothermia. Technology to miniaturize the cir-

Table 2. Factors Contributing to Death (n = 135)

Factor	No. of Patients	Percent
Cardiac	101	74.8
Pulmonary	30	22.2
Central nervous system	37	27.4
Bleeding	35	25.9
Renal	1	0.7
Other	22	16.2

Adapted from Hill JG, Bruhn PS, Cohen SE, et al. Emergent application of cardiopulmonary support: a multiinstitutional experience. *Ann Thorac Surg* 1992;54:699-704, with permission.

Table 3. Morbidity in 105 Patients

Morbidity	No. of Patients
Vessel cannulation	
Femoral artery repair (required)	4
Femoral artery occlusion	1
Femoral artery pseudoaneurysm	3
Large hematoma	4
Thrombophlebitis	5
Cannula site infection/necrosis	8
Femoral nerve injury (transient)	2
Embolism	
Superior mesenteric artery embolus/thrombus	1
Cerebrovascular accident	1
Transient cerebral ischemia	1
Angioplasty	
LV dysfunction requiring balloon pump	1
Post-PTCA myocardial ischemia	5
Post-PTCA myocardial infarction	7
Cardiac arrest	1
Other	
Gastrointestinal bleeding	2
Diabetic ketoacidosis (bowel ischemia)	1
Acute renal failure	1

LV = left ventricular; PTCA = percutaneous transluminal coronary angioplasty.

Reprinted from Vogel RA, Shawl F, Tommaso C, et al. Initial report of the National Registry of Elective Cardiopulmonary Bypass Supported Coronary Angioplasty. *J Am Coll Cardiol* 1990;15:23-9, with permission from the American College of Cardiology.

cuitry to make it more biocompatible and less expensive is available. Whether or not the technology will become distributed to the hands of those using and needing it will depend on the economic pressures of supply and demand. In the meantime, the equipment that is readily available today can be successfully used for patient care only when it is combined with an organized, carefully considered team approach.

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Pharmacological Bridge to Cardiac Transplantation: Current Limitations

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Addition of intravenous enoximone to sympathomimetic agents permits a rapid and drastic improvement in the clinical and hemodynamical condition of patients in cardiogenic shock referred for a mechanical bridge to transplantation. The present experience, based on the management of 52 patients, permits us to point out the

current limitations of this pharmacological bridge: the rate of sudden death, the incompleteness of the physical rehabilitation of the patients, and the vanishing effect of intravenous enoximone.

(Ann Thorac Surg 1993;55:310-3)

A mechanical bridge has been proposed for patients in cardiogenic shock who are unresponsive to optimal medical therapy based on sympathomimetic agents. These patients may be patients whose condition is deteriorating while they are waiting on the transplant list or those referred acutely for an immediate transplantation. The addition to the widely used medical therapy of intravenous enoximone has been shown to improve immediate survival [1] and to reduce the need of mechanical circulatory support and, consequently, the cost of the management of such patients [2]. The present pharmacological strategy gives time for a reevaluation of the indications for the transplantation, thus permitting the saving of grafts. It permits the discovery in a less emotional context of hidden contraindications. It also gives an alternative to those patients, refused for transplantation, who will otherwise die.

The pharmacological bridge strategy, consequently, satisfies both the patient's instinct to stay alive and, at the same time, society's concern about the cost and cost-effectiveness of health care in acutely ill patients.

The present work, which is based on the experience obtained in 52 patients, points out the current limitations of the pharmacological bridge strategy.

Clinical Material

The 52 patients considered for the study entered the protocol from January 1986 to September 1991. Four were previously selected for cardiac transplantation (HTx) and were referred because of acute deterioration while waiting on the transplant list. Forty-eight were acute patients referred from various intensive care units in France. Mean

age was 51 years (range, 22 to 64 years). There were 46 men and 6 women. Duration of the period of sympathomimetic support before the start of enoximone therapy was 15 hours, ranging from 2 hours to 4 days. Cause of the cardiopathy was ischemic in 22, including 15 with acute myocardial infarction, valvular in 2, dilated cardiomyopathy in 25, acute rejection in 1, and acute viral myopathy in 2.

The detailed protocol has been previously published [1] and is illustrated schematically in Figure 1. The criteria for inclusion in the protocol included clinical evidence of cardiogenic shock, confirmed by hemodynamic data (cardiac index $< 2 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$, mean aortic pressure $< 75 \text{ mm Hg}$, pulmonary capillary wedge pressure $> 25 \text{ mm Hg}$), obtained under maximal sympathomimetic support and optimal medical management. Only patients with no contraindication to transplantation (age > 65 years, diabetic, cancer, infection) were included. Indication for mechanical circulatory support was the lack of improvement in hemodynamical indices and rhythm complications.

Results

After the first intravenous enoximone injection the clinical and hemodynamical situation (Table 1) was dramatically improved in 44 patients. The most spectacular change was the increase in urine output, even in patients previously anuric. In 8 patients, no improvement was observed within the first 30 minutes of observation. In addition, rhythm troubles occurred, with ventricular tachycardia and fibrillation in 3 patients. Conventional resuscitation maneuvers including rapid institution of cardiopulmonary bypass (in 2) were successful in all. These 8 patients were eligible for the mechanical bridge strategy. In the 44 patients responsive to enoximone, enoximone bolus was repeated every 8 hours.

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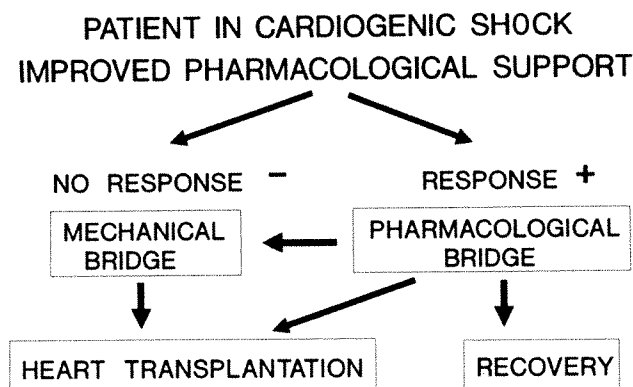


Fig 1. Schematic representation of the protocol.

Mechanical Bridge Patients

The type of mechanical circulatory support system that was used was a Jarvik 7-70 in 3 patients, a Symbion left ventricular assist device in 1 patient, biventricular assist devices in 3 patients (Symbion in 2, Nippon Zeon in 1), and a Novacor left ventricular assist system in 1 patient. The mechanical circulatory support system was connected in all patients but 4 (the patients with ventricular assist devices) under cardiopulmonary bypass. Selection of the device was made in the operating theater using clinical, hemodynamic, and echocardiographic (in the last 3 cases) evaluation of the right ventricular function.

Improvement of hemodynamic condition was spectacular in all but 1 patient, because of a progressive loss in vascular tone on day 3. Organ function did not recover in 2 patients. In addition, the condition of the patient stable on the Novacor left ventricular assist system deteriorated suddenly after 9 days, due to a recurrence of acute myocardial infarction in the right ventricle. Five patients could undergo transplantation after stabilization on day 5 (range, 3 to 12 days). Two died after heart transplantation owing to irreversible multiple organ failure. One died of septic shock while on dialysis on day 9 after transplantation.

Pharmacological Bridge Patients

The 44 patients who initially improved had a variable evolution. The condition of 13 patients deteriorated after 7 days (0.5 to 14 days), and in 31 patients the hemodynamic situation either stabilized or improved dramatically, mak-

ing possible either weaning off drugs or transplantation on an elective basis. As a whole, the results are as follows.

In 12 patients, a contraindication led to the postponement of transplantation. This decision was made in 15 days (range, 2 to 43 days), because of cancer, epileptic seizures, sepsis, chronic alcoholism, poor compliance, and a complex social environment. Four died within a month, because of sepsis in 1, brain tumor in 1, and multiple organ failure in 2. The others could be discharged and kept alive in New York Heart Association functional class III under oral medication. Eight were still alive at 1-year follow-up. In 1 patient, the improvement in the familial and social environment led to a reconsideration of the previous decision. The patient underwent transplantation and died of pulmonary infection after 6 days.

In 6 patients who initially improved hemodynamically, the lack of rapid recovery of organ failure led to contraindication of both implantation of a mechanical circulatory support system and in 3 patients transplantation itself. In 3 patients, the transplantation was performed, as a life-saving procedure, within 4 days. Only 1 patient survived. The 2 others died because of multiple organ failure in 1 and graft failure in 1.

In 26 patients, indication for cardiac transplantation was reconfirmed within 14 days (range, 0 to 95 days). The condition of 4 patients deteriorated suddenly, because of ventricular fibrillation in 1 and electromechanical dissociation in 3. Only 1 could be implanted with a Jarvik. His condition deteriorated rapidly due to loss of vascular tone. In 14, the transplantation was performed after 11 days (range, 0.5 to 27 days). Nine patients could be discharged. In 8, the lack of organ available and the continuous improvement of clinical condition led to their discharge. In 3 patients the transplantation was performed successfully after 75, 102, and 181 days. Two patients died suddenly while waiting for transplantation at home, after 42 and 161 days. In 2, the indication for transplantation disappeared. One is still on the list after 5 months.

In the present group of 26 patients reconfirmed for transplantation, an index of risk of death of patients treated in the intensive care unit (SAPS index [3]), based on 14 easily measured biological and clinical variables, was computed on the day of institution of intravenous enoximone therapy and the day of transplantation (in 14).

Table 1. Hemodynamic Changes After Intravenous Enoximone Bolus Injection

Time (h)	Urine Output (mL/h)	Heart Rate (beats/min)	MAP (mm Hg)	PAP (mm Hg)	PCWP (mm Hg)	Cardiac Index ($L \cdot min^{-1} \cdot m^{-2}$)	SVR ($dynes \cdot s \cdot cm^{-5}$)
0.00	38.82 $\pm$ 4.68	104.21 $\pm$ 2.68	73 $\pm$ 3	50.91 $\pm$ 2.52	28.65 $\pm$ 1.43	1.71 $\pm$ 0.07	1,594 $\pm$ 95.15
0.30	87.86 $\pm$ 4.92	102.04 $\pm$ 2.40	72 $\pm$ 3	47.07 $\pm$ 2.24	21.50 $\pm$ 1.38	2.66 $\pm$ 0.13	1,176 $\pm$ 80.03
2.00	87.92 $\pm$ 5.32	101.54 $\pm$ 3.65	71 $\pm$ 3	42.87 $\pm$ 2.11	20.25 $\pm$ 1.64	2.53 $\pm$ 0.11	1,226 $\pm$ 89.95
4.00	95.00 $\pm$ 3.45	97.78 $\pm$ 5.05	73 $\pm$ 3	47.22 $\pm$ 2.50	24.83 $\pm$ 1.81	2.46 $\pm$ 0.11	1,249 $\pm$ 85.48
8.00	90.91 $\pm$ 5.18	102.68 $\pm$ 3.30	74 $\pm$ 2	51.50 $\pm$ 2.31	25.77 $\pm$ 1.72	2.10 $\pm$ 0.15	1,464 $\pm$ 121.33

MAP = mean radial artery pressure; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; SVR = systemic vascular resistance.

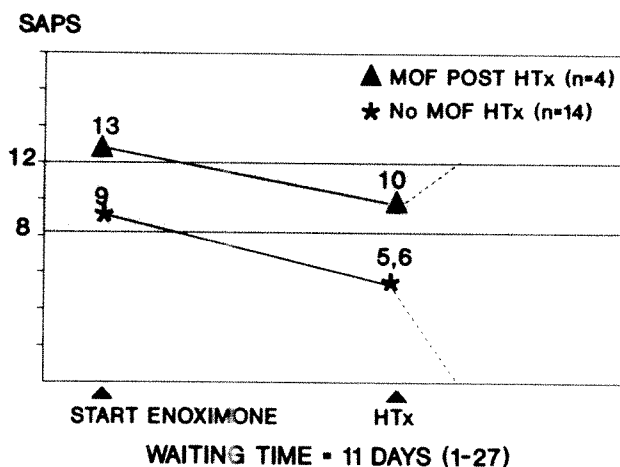


Fig 2. Evolution of the SAPS index in the group of patients reconfirmed as good candidates for transplantation during the waiting period. Patients who will die after transplantation owing to multiple organ failure (MOF) (▲) have been transplanted after an incomplete improvement of the SAPS index. Patients who will be free of any organ dysfunction after transplantation (★) were more improved while waiting for the graft. The shaded area represents the value of the SAPS index, which has a low prognostic value.

The mean values of patients who will be successful or who will die of multiple organ failure are represented in Figure 2.

As a whole, at 1 month, 29 patients were alive (55%); 13 underwent transplantation, 3 after a mechanical bridge and 10 after a pharmacological bridge. Eight are still waiting for the transplant and are stable at home. Eight patients with some type of contraindication are in stable condition on oral medical therapy. At 1 year, 19 patients were alive (37%), with 13 receiving transplants after a mechanical (in 2) or a pharmacological (in 11) bridge. Two are in stable condition and New York Heart Association class I; they were withdrawn from the transplantation list because of spectacular ventricular improvement. Four patients with a contraindication are still living on medical therapy.

Comment

A few comments are necessary for a better understanding of the present strategy. First, the concern about the cost-effectiveness of the management of the patients about to die is a situation imposed by the present expectations of society and the various institutions involved in payment for health care. The second comment is about the origin of the patients admitted in cardiogenic shock who may be candidates for a mechanical bridge to transplantation. Most are not, in our experience, patients whose condition deteriorates while they are waiting for cardiac transplantation. This is due to the policy of our institution based on the most urgent-first served principle. This might also be due to the care given in the evaluation of prognostic indices in the transplant candidates. The selection is based on analysis of metaiodobenzylguanidine cardiothoracic ratio [4]. The relatively high

number of urgent patients referred for immediate transplantation or mechanical bridge may also be the result of the position of Henri Mondor's hospital, to which a third of the cardiac emergencies of the whole Parisian area are referred.

The previous publications [1, 2] of our group have emphasized the benefits of the pharmacological bridge strategy in terms of cost savings, cost-effectiveness, and saving of cardiac donor grafts. The present report focuses on the limits of our strategy.

The limits of the strategy are obvious. The outcome of the 3 patients of 8 who are unresponsive to enoximone and who received a mechanical circulatory support system is unsuccessful, owing to loss of vascular tone and irreversible multiple organ failure. The loss in vascular tone has been related to a consequence of prolonged pharmacological support [5]. The irreversible evolution of organ failure has been shown to be more frequent in patients implanted late [6]. The limits of the strategy are also obvious in the patients initially dramatically improved within the first 8 hours of intravenous enoximone. Two different modes of failure may be considered: sudden death and poor physical rehabilitation during the waiting period.

The rate of sudden death appears unacceptable in the group of patients reconfirmed as good candidates for cardiac transplantation. Four of the 26 patients (15%) died as they were waiting in the intensive care unit for a suitable graft. In addition, 2 died suddenly in the group of 8 patients successfully discharged from the hospital. Adequate management of such an acute complication is most difficult, and resuscitation procedures are unlikely to be successful. The risk of failure of the pharmacological bridge appears to be unacceptably high in the group of ischemic patients [7].

The second problem is related to the incompleteness of physical rehabilitation of the patients improved hemodynamically by intravenous enoximone. In the group of patients who could not be discharged, the SAPS index clearly shows that the situation at the day of transplantation is not optimal. The unacceptably high number of patients dying within a month after transplantation because of multiple organ failure is probably a consequence of the incomplete rehabilitation. This observation has to be considered when the time required to obtain a suitable donor is increased. It should lead to implantation of a mechanical system, permitting prolonged and safe waiting time.

The present experience, obtained in the management of a substantial number of patients, helps the evaluation of the real role of pharmacological bridge in the management of the patients in cardiogenic shock who are candidates for cardiac transplantation. The data show clearly that there are indications of mechanical devices, because of the limits of the pharmacological bridge, both at the time of admission and after a few days.

In conclusion, the present limitations of the pharmacological bridge pointed out in the present study should not cause one to underestimate the benefits developed previously. They emphasize the problems encountered in daily

practice, when attempts are made to offer the patient the most cost-effective management.

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FDA Regulatory Issues Session

How Much Do We Need to Know Before Approving a Ventricular Assist Device?

Moderator: J. Donald Hill, MD

Panelists: Bette Lemperle, BSN, MPH, Mark Levinson, MD, Victor L. Poirer, BSME, and Bartley P. Griffith, MD

MODERATOR HILL: Each of us here has a different role to play in how to help patients in the very best way. The goal here today is to have a dialogue among these various interests to discuss the motives, goals, responsibility, and accountability involved in developing a ventricular assist device to the point where it can be successfully used in our patients. It is a complex issue that has evolved through the years. But it is one we must work through, we must understand, and we must solve so we can make these devices safe, effective, cost-efficient, and helpful for our patients.

There are various interests in society that address this issue, and each has its own different viewpoint. First are those in medicine, who are the advocates of the patients and are doing everything possible to help them. Then there is the Food and Drug Administration (FDA), which regulates devices and is held accountable by society to make sure they are safe and effective because patients themselves are not in a position to judge that. Next, there is industry, which has a responsibility to both society and its shareholders. Then, there is the National Institutes of Health, which, although not always in the loop, is accountable for rigorous research on these devices to make them worthwhile for society. And finally, there is the patient. We must never forget that it is the patient for whom we all are really working. We have to be accountable to patients, as well as ourselves. Together, through dialogue and compromise, we can determine how best to solve this complex issue.

With that short introduction, let us begin with four presentations. Each represents one of these different segments of society and will cover its role and responsibility in the process. The model we develop now for some of these life support systems will be one we use in the future, so it is crucial we do it well and everyone be properly represented so that it is the patients who ultimately benefit.

To begin is Bette Lemperle, who represents the FDA.

BETTE LEMPERLE: Thank you for inviting me to present the FDA's view on the topic "How Much Do We Need to Know Before Approving Ventricular Assist Devices?" This subject has been on the minds of many people involved in this type of work for several years.

Indeed, many suggestions are offered in this regard, particularly at meetings such as this one. Some of you have suggested that there should be a provision for the use of prototype devices in up to 200 patients before the FDA ever gets involved in an investigation or approval. Others have suggested a more modest number of 7 or 10. Still others suggest that although early FDA involvement with new devices is warranted, it is sufficient for us to know that a device meets certain test parameters in the laboratory and in animals, and that as a pump it pumps without failing in the clinical setting.

Although there is general agreement with the basic principles underlying the FDA's oversight of clinical research, not everyone agrees on how these principles should be translated into the specifics of how much in vitro testing is sufficient, how many animals should be tested with the device, what are the appropriate patient selection criteria, how success should be defined in the clinical trial, what end points should be measured, and what is an appropriate follow-up protocol.

In the early days many investigators, enthusiastic about these new systems, viewed them first as potentially life-saving therapy for their dying patients, with data collection and protocol compliance being distinctly secondary concerns. Potential investigators did not appreciate the FDA's role in limiting the availability of these, yet unproven, investigational devices. There was resistance to the FDA insisting on a degree of uniformity in study protocols and data collection to decrease the potential for bias. The FDA, on the other hand, contended that by not conforming to these requirements, investigators were adding to the delay in getting potentially useful devices to the market and available for wider use.

The FDA has attempted with some success to address these issues through a continuing dialogue with the clinical investigator community and the professional societies. As a result of this cooperative dialogue, the scientific documentation of the clinical safety and effectiveness of these devices has evolved to a point where market release of one or more short-term use ventricular assist devices (VADs) appears to be near.

In a group such as we have assembled here, there are usually many people who are unfamiliar with the law and regulations governing FDA device review and approval. Therefore, before proceeding with the discussion of the type of data that we require to demonstrate safety, effec-

tiveness, and clinical utility of the VAD, I will briefly summarize the aspects of the Medical Device Amendments of 1976 and the Safe Medical Devices Act of 1990 that are pertinent to this discussion.

The Medical Device Amendments of 1976 established a three-tiered system for regulating devices. The Safe Medical Devices Act of 1990 further defines the system. In the three-tiered system each tier, or class, is based on the extent of control necessary to reasonably assure the safety and effectiveness of the devices. Class I devices, such as the surgical scissors and manual stethoscope, are only subject to general controls, such as good manufacturing practices, quality assurance in manufacturing, and labeling. Class II devices such as x-ray and ultrasound equipment can be marketed subject to general controls and special controls such as compliance with voluntary or mandatory performance standards, postmarket surveillance, and additional preclinical and clinical performance data requirements that the FDA may consider necessary. Class III devices such as heart valves and implantable defibrillators are life-sustaining or life-supporting devices for which general controls and special controls are insufficient to assure safety and effectiveness and which, therefore, must undergo the premarket approval process. Total artificial hearts and ventricular assist devices fall within the class III regulatory category.

Regulations developed to enforce these laws provide for three types of medical device applications to (1) legally market the device, (2) conduct a clinical investigation of a device, and (3) seek approval to market a device. The applications include the Investigational Device Exemptions (IDEs), the Premarket Approval Application (PMA), and 510(k) or premarket notification. 510(k)s are not applicable to VADs at this time. Investigational Device Exemptions are intended to study the safety and effectiveness of medical devices in humans after sufficient preclinical data demonstrate the relative safety of the devices. For certain class III devices, the manufacturer submits the preclinical and IDE data in a PMA application. The PMA application is reviewed by FDA scientists, and it may be submitted to an advisory panel at the FDA's discretion. Advisory panels, which are composed of physicians, scientists, consumers, and industry representatives, regularly assist the agency by making recommendations on the safety, effectiveness, and clinical utility of new devices. Their participation in the approval process adds a critical perspective from the academic community and the everyday world of medical practice as a complement to the FDA's scientific and technical review. The PMA application process allows the agency to determine if a class III medical device has been shown to be reasonably safe and effective for its intended use, and therefore suitable for marketing.

Mandates of the Act and subsequent regulations require that clinical trials on medical devices meet certain standards for the protection and welfare of human subjects and for the orderly collection of clinical data. The three basic requirements are as follows: (1) A risk-benefit analysis, based on objective criteria, must demonstrate that the benefit to the individual patient in terms of likely

therapeutic value, and to society in terms of knowledge to be gained, outweighs the foreseeable risk to the patient. (2) Informed consent is to be obtained. (3) An Institution Review Board and the FDA provide peer review of the proposed clinical trial. These are the requirements of good science and good clinical research, not unlike those imposed by the NIH for funding clinical research, and are derived from landmarks such as the Nuremberg Code, the Declaration of Helsinki, and the Ethical Guidelines Statement of the American Medical Association.

In carrying out these requirements, the FDA looks closely at the safety, effectiveness, and clinical utility of the VAD systems that are proposed for premarket approval. During the early years of these clinical trials, the FDA did not play a very active role in attempting to define clinical protocols for data analysis strategies. The focus of our review was on the rationale for the device design, assessment of the compatibility for blood- and tissue-contacting materials, evaluation of design material factors such as resistance to thrombus formation, evaluation of potential causes for damage to blood components, characterization of the device, assessment of device durability and reliability, and its performance in vivo. This was a learning period for sponsors, for investigators, and for the FDA. Many new and unique questions and concerns were addressed and procedures and policies were progressively developed. The sponsors were relied upon to do what was necessary to optimize the scientific yield from the clinical trials.

The same type of preclinical data are required today, and the FDA must determine that these data are acceptable before approving a PMA. The questions that come up most frequently in regard to preclinical data are the FDA's requirements for in vitro and animal testing. I will briefly summarize these requirements.

All preclinical testing required for circulatory assist devices must be performed on the final clinical design to be used in the clinical trial. When the information is submitted, the FDA expects it to be comprehensive and collected methodically according to established norms of good clinical science. The FDA also expects the results to be appropriate for the intended use of the device and to demonstrate reasonable assurance that it will perform safely in the proposed clinical population. In vitro studies encompass materials testing, flow visualization, design validation, and device characterization. The device characterization study must include the data collected under an orderly array of conditions that represent the total range of conditions that could occur during clinical use of the device. This would include (1) use of the system in all modes of synchronous and asynchronous operation; (2) the value ranges required to attain the cardiac outputs anticipated in the clinical setting such as air pressure, beats per minute, right and left atrial pressures, and percent systole; (3) peak pressure gradients across the valves and peak pressure at the exit ports for each cycle for each parameter range; (4) parameters of operation under worst-case physiological conditions, that is, the highest flow and lowest flow under which the pump can operate and threshold conditions that will cause the

pump to fail; and (5) Starling's curves for operation of the device.

The durability and reliability testing includes (1) a description of test results for a minimum of eight systems, of which four are removed and examined after 6 months and four are allowed to run to failure. The system should be run under worst case and normal conditions based on the results of the characterization study. (2) The model used to predict reliability must be presented also. Currently 80% reliability with a 95% confidence or better is acceptable. (3) The results of the study must include a detailed examination of all components for wear and cracks, with special emphasis on the diaphragm and the valves. These components should be examined by scanning electron microscope, thermal imaging, and other high-magnification examinations. In addition, information on fatigue, the predicted life of the system, the predicted life of critical components, and the maintenance schedule based on all of these factors is required. (4) All failures must be described including when they occurred, why they occurred, whether they could be resimulated, whether the component could be changed, the potential effect of a failure on the clinical situation, whether the reliability test was continued after failure, and the actions taken to prevent their recurrence.

To satisfy our in vivo requirements, a minimum of 8 animals must have the device implanted for at least 4 months. The primary objective of the in vivo evaluations is twofold: first, to observe how the device performs in the physiologic environment that is similar to clinical use, and second, to observe the physiologic changes that occur in response to the implant. A secondary objective of the in vivo study is to confirm the findings in the in vitro tests. In this regard, the FDA expects to see the devices used in the animal studies explanted and evaluated for wear. The FDA also requires hematology and blood chemistry study results for each animal and for all animals including the mean preimplantation and implantation parameters at regular intervals for the period of implantation; complications that occurred during each animal implantation and a summary of the rate of occurrence of each type of complication for the group; and reports of explanted devices for each animal with diagrams and photographs as necessary to illustrate the appearance, results of microscopic examination of component wear and deterioration, a description of the location and size of thrombus formation, and results of histopathological studies. Autopsy reports should also be provided for each animal, with pictures of the device in situ, autopsy examination with conventional histological studies of major organs, and histological evaluation of all areas of grossly evident pathology. We would also want information on changes made to the device or to the proposed clinical trial based on the results of the animal study.

Occasionally, study sponsors will inform the FDA that the animal model is not appropriate for evaluating clinical readiness of their device. The FDA will consider documentation supporting this position. However, there have been studies where adverse effects that occurred during the animal trials were attributed to the animal model, but

when the clinical trial was subsequently initiated, these same events that had been attributed to the animal model were replicated early in the experience. So animal trial findings continue to be an important feature in judging the clinical readiness of a device.

About 5 years ago it became clear to the FDA that its prior policy of relying on sponsors and investigators to do what was necessary to optimize the scientific yield from the clinical trials was not sufficient to move the studies toward premarket approval. Study sponsors were not defining, directing, or monitoring their studies with the kind of control and goal orientation necessary to develop scientific data for eventual determination of safety, effectiveness, and clinical utility. After consulting with the scientists and clinicians in the Center for Devices and Radiological Health, members of the Circulatory System Devices Panel, and consultants from other medical device panels, it appeared that the data being submitted to the FDA were preliminary and could best be used as baseline information for formulating questions to be answered about clinical effectiveness and utility in appropriately designed second-phase clinical trials.

The FDA maintains that a pilot study is valuable and that a second-phase trial with experienced investigators implanting devices in appropriate patients can be conducted expeditiously. The anticipated results are data of a quality suitable for a final analysis to determine VAD safety and effectiveness as a bridge to transplantation or for weaning from bypass. Some sponsors have completed this process, and an earlier satisfactory overall conclusion to the evaluation of their experience is anticipated despite their initial frustration.

From the inception of the IDE, new study sponsors are encouraged to design studies using sound scientific principles. Some of the items that must be addressed are: (1) What are the questions that need to be answered about a device and the effect on an intended population? Specifically, what do we expect the device to do? What patient population do we target? How do we define that patient population? (2) We need to know the general and specific study objectives based on these questions. For instance, in the postcardiotomy patient we would want the sponsor to demonstrate that the device can provide effective hemodynamic support, that it allows for myocardial recovery, and that it allows for survival in 20% to 30% of the patients who meet the selection criteria. (3) We need to know how success or failure of study objectives will be demonstrated. For instance, how is the device expected to perform hemodynamically in the patient? How will vital organ function be measured? How is the control group defined? What types of adverse events are anticipated? What rate of adverse events is acceptable? What number of study patients and control patients is necessary to demonstrate safety and effectiveness? What number of centers will be needed to obtain the data in a reasonable period of time? What controls will be instituted to address the inclusion of multiple centers? How long should patients be followed up? What data should be collected during follow-up? (4) What specific data parameters will be collected to demonstrate success or failure? How will

the data be normalized to address the differences between the centers? What type of format will be used for recording the information? (5) Finally, what type of analysis will be performed on the data, and what statistical methods will be used in the analysis?

The FDA expects sponsors to establish continuity between the questions to be answered, data to be collected, the size of the study, and all the steps leading to the proposed analyses. Otherwise, conclusions drawn from the study may be unacceptable.

Control or reference group data are essential and should be collected from the outset of clinical implantation. If patients are their own controls, as is common with the VAD weaning indication, time frames for attempting weaning with drug therapy and intraaortic balloons before VAD therapy must be established and adhered to. The assumption is that before entrance into the study, no apparent irreversible end-organ function has occurred and the device may be evaluated by its ability to maintain appropriate pressures, flows, and patient hemodynamics; to protect end-organ function; to promote myocardial recovery; and thereby to promote survival. With the bridge indication, the FDA expects clinical centers to track transplant patient populations who meet the same study entrance criteria as bridged patients but do not receive the bridge device.

Uniform study criteria, entrance criteria, procedures, and interpretation of adverse events are essential for both intracenter and intercenter pooling of data. Justification must always be given for pooling among study centers. With a large number of study centers and investigators in VAD studies, uniformity becomes a critical issue in judging pooling of data for analysis. For example, data have been reviewed by the FDA where as many as half of enrolled patients did not meet entrance criteria. This can be attributed in part to the tendency of some investigators to reason that if the device has worked well for long periods to bridge patients who meet standard heart transplant criteria, perhaps it will work well in patients who do not meet transplant criteria, reversing severe end-organ dysfunction and thus allowing sufficient recovery to permit transplantation weeks or even months later. This may be true, and may identify a subsequent group of patients to be studied. The problem is that by adding a new group of patients, a separate study has been initiated before the original questions have been answered, and it is likely that both study and premarket approval will be delayed. Indeed, just how much clinical data will be required to approve a VAD is greatly related to the number of VAD study patients and control patients entered into the study who meet study entrance criteria and the difference in outcome between these groups. If most of the patients implanted with the device do not meet entrance criteria and control data are not collected, the final results cannot be evaluated.

Both bridge to transplantation and recovery protocols currently require patients who enter these studies to have adequate end-organ function or dysfunction considered reversible. This is needed to assess the effect of the device on end function. Every attempt should be made to accu-

rately document end-organ function before device implantation. Consequently, when a patient is on a device beyond the time it normally takes to recover from the effect of cardiopulmonary bypass and other hematological insults, hematology and blood chemistry parameters that reflect end-organ function status are expected to be maintained at reasonable levels or improved as compared with preimplantation levels. Therefore, patients with irreversible end-organ function are not eligible for these studies, and if they receive implants as emergency use protocol deviations, their data should be analyzed separately from the core patient group.

Another uniformity issue concerning study entrance criteria is defining heart transplant candidates. When bridging was initiated in 1985, each heart transplant center's criteria for transplantation were based on the Stanford criteria, and criteria varied little from center to center. At that time it was sufficient to state that patients who met the center's heart transplant criteria could be entered into a bridge to transplantation study. Today, however, transplant criteria vary from center to center, and it is no longer sufficient, in a multicenter study, to state that a patient may enter the study after meeting the heart transplant criteria at his or her center. Study entrance criteria must incorporate those heart transplant criteria that define a specific study population. This does not mean that all centers must use the same heart transplant criteria as those specified for the study. Rather, only those patients who enter the study must meet the same transplant criteria.

Evaluation of adverse effects also has limited utility when each event is not specifically defined. Although accepted uniform definitions are lacking within the medical community at this early stage of the technology, each investigator must have a basis for making a declaration about an event that ensures conformity or at least comparability with such decisions at other study centers. Definitions developed for these early studies may well be the basis for generally accepted definitions across all VAD studies in the future.

The issue of uniformity extends to implant procedures, patient management, autopsy protocols, and explanted device analyses. When uniform procedures are not followed, the reason must be documented. This information is extremely important to the overall analysis.

In addition to appropriate study design and procedures to assure collection of reliable data, the FDA has also focused attention on actual data collection used to evaluate study end points and to answer the important questions about device function in the indicated patient population. For valid conclusions to be drawn, these data must be collected for all patients at specific times in the same manner. Otherwise, use of the most appropriate statistical methodology to support a conclusion is worthless. If the study is supposed to demonstrate that the device can increase cardiac output to levels consistent with survival in hemodynamically compromised patients, data must be collected to demonstrate patients' hemodynamic parameters before implantation and at regular intervals subsequent to implantation. Similarly, to dem-

onstrate that the device does not cause hemolysis, kidney failure, or untoward neurological effects, data must be collected for baseline information before device implantation, during device use, and after removal. When data are aggregated to demonstrate device effects on patients, only data for those patients for whom all of the data were collected can be used in the analysis. Sometimes data from autopsy reports or device analysis studies are used to demonstrate that a particular anticipated effect or patient injury was not observed in the study. Such data must be qualified with information on the number of autopsies and device analyses that were actually performed. For example, if 10 patients die, but only two autopsies are performed, less weight is given to the findings.

These are just a few of the examples of VAD protocol and data issues with which the FDA has been grappling in the regulatory role. There has been progress amidst these many complexities, and it is anticipated that the Circulatory System Devices Panel will soon be evaluating data in preparation for making recommendations on several systems currently under study.

MODERATOR HILL: We will have the discussion immediately after each presentation, so that if there are questions on people's minds directly pertaining to the presentation, they can bring them up while they are fresh in everybody's mind. Are there any questions that anybody would like to bring up or discussion points on the presentation?

DR WILLIAM L. HOLMAN (Birmingham, AL): The implication of your talk was that any compassionate use outside of protocol will actually delay the approval of the device. Did I understand that correctly?

MS LEMPERLE: Well, the data cannot be used in the analysis. So that would be collecting data that are not usable. They can be used to a certain extent, but not in the core analysis to substantiate effectiveness.

DR HOLMAN: Okay. Just what is the FDA's general view of compassionate use of these devices? I will give you an example. Suppose you have a patient who has had a pulmonary embolus, and pulmonary embolism in your institution is considered a contraindication for transplantation unless you can document resolution of the embolus, which usually takes several weeks. Therefore the patient falls outside of protocol. He or she is not at the time that you need the device a candidate for transplantation. It is that kind of situation that we deal with from the standpoint of clinicians. The patient is going to die, but is outside protocol. Should you use the device even though the data cannot be used? What is the FDA's feeling about that? If we use too many, are we going to have a problem with the FDA?

MS LEMPERLE: We leave the decision as to whether you can use the device or not up to the sponsor of the study. It is their study. They have to get the data. But

when we evaluate the data and we see that none of the data from some investigator can be used in the study, we might question why they would want to keep that investigator in the study.

SPEAKER: Does the FDA differentiate between data collected in Europe or the United States? If there is some modality used in Europe earlier than in the United States, do the data add to the collection in the United States?

MS LEMPERLE: It would depend on the situation. There are occasions when European data are used for a PMA. But generally the data for an IDE are collected in the United States. The problem is that we have to demonstrate that the patient populations are identical, that the protocol was followed, and that informed consent was collected. And that is often difficult to collect in another country.

DR ERIC A. ROSE (New York, NY): You state, I think quite legitimately, that a risk-benefit analysis is an important part of your assessment of the appropriateness of a clinical protocol. It seems that the FDA is beginning at least to consider risk-benefit analysis in terms of the stringency of its regulation of introduction of new technologies as well for certain disease states. We see that now drugs for human immunodeficiency virus and drugs for malignancies seem to be fast tracking through your system. One does not get the sense that type of fast track yet exists in the field of end-stage heart disease. Could you comment on that? Do you have the perception that a risk-benefit analysis should be appropriate for device approval in this area of end-stage heart disease?

MS LEMPERLE: I would think that your interpretation is correct; it has not reached down to this area and we have not discussed it yet.

MODERATOR HILL: The next speaker is Mark Levinson, who is a surgeon and a member of the FDA's Circulatory System Devices Panel.

DR LEVINSON: My particular role in this is as a member of the Circulatory System Devices Panel. This panel consists of physicians who act in an advisory capacity to the agency at the time of premarket approval. For those of you who are not familiar with my background, I am currently a cardiovascular surgeon practicing in Seattle. My training in devices took place primarily at the University of Arizona. After leaving Arizona, I was invited to be a member of this panel in about March of 1988. Subsequently, I have had the chance to review applications for various types of medical devices in my specialty such as cardiac valves, vascular grafts, pacemakers, laser angioplasty, and atherectomy devices. We are now entering an era when we are going into the complexities of circulatory assist devices.

I thought I would just review some of my own experiences. The Circulatory System Devices Panel is a limb of the agency that attempts to inject some peer review or

physician review into this approval process. The FDA, itself, is a regulatory agency created by consumer law. I have detected a lot of feelings in this audience in the last few days about how difficult it is to get devices through to final market. But the fact is that this frustration is a direct result of our own legislation in this country, and has been driven by the legal profession and consumer law. We now have to administrate this law as effectively as we can. It is intended to reduce victimization of the patient by devices that are incorrectly designed, inappropriately marketed, or in some cases, are frankly irresponsibly created. The Circulatory System Devices Panel attempts to inject its practice patterns and its feelings about device safety and effectiveness into this process. Often I call on myself to ask this important question: "Would I let someone implant this device in my own father?" And if I believe it is safe and effective, then I am generally able to answer that question affirmatively and vote for approval.

The panel has been asked to make its decision on what has been termed as "valid scientific evidence" of safety and effectiveness. A standard has been set up in the agency that this should take place through a prospective clinical trial. There are a lot of other strategies, but a clinical trial is the standard by which we base our decision. We are not able to use peer review literature, case reports, anecdotal experiences, or even the market history of the device in other countries as reported through peer literature or personal experience to approve these devices. There must be a prospective trial. So in a sense that trial becomes the most important document in making these decisions.

I think from the sponsors' standpoint, you must understand that the panelists see this document at the end of your second-phase IDE trial. Essentially, we are injecting ourselves late in the development of this trial. The only thing we are expected to evaluate is the document itself, so the organization of that document and the quality of the materials in that document will determine how we interpret it.

Another thing that I often emphasize to sponsors is that the burden of proof rests with you. It is not up to me to find the material that has been held back, or the missing data. We will just be left with inadequate support for this decision. The burden of proof rests with the sponsor, and that is often lost in the morass of these trials.

Let me just discuss a little bit about the guidance document that is often mentioned. The FDA has attempted to provide a rough framework for structuring these protocols. I think Bette Lemperle has given an outstanding summary of what the current viewpoint is on circulatory assist devices. But I would like to stress that the guidance document that is currently available is preliminary. It is not a final version, and even so, with the final version, this is intended to be a framework. The panel will often insist on even more than is in that guidance document. We have seen sponsors who have said to us that we are asking for data that was not requested in the original guidance. And yes, that is absolutely true. The guidance is a rough skeleton upon which to build a good clinical trial. I think that you should

always consider building upon that. If you fail to capture pertinent data early in the trial, the opportunity to analyze them and to reach conclusions from those data is lost. And after studying 100 or so patients, if some vital information is not included in the initial trial, all of that effort will be wasted.

Let me talk a little bit about protocol structure. I mentioned that we are very, very dependent on the final PMA submission during the approval process. I will say that in device technology, it is important to very intensively survey a small number of patients for a short time. We will never see a large series with these devices. So, the intensity with which you survey the patient is going to increase the information quality that we get when you submit the device for panel review. Thus, the protocol has to be set up well and it is very, very helpful to involve your principal investigators in the design of the study.

I was struck by Peer Portner's slide this morning when he described his steering committee in setting up the NIH clinical trial for the long-term implantation of the Novacor device. I think this approach is essential and yet often neglected. Usually I see companies who have charged their vice president of regulatory affairs with coming up with a protocol that will satisfy the FDA. This may not satisfy physician panel needs four years later. Involve the physicians early and continuously, and get their feedback. If they need certain parameters in that trial, find a way to get them. Physician panelists in the same related specialties four years later are going to be asking for that information, and if it is missing, it really will cut down on the quality of our analysis of that study.

Another important point is to keep in frequent contact with the agency. Bette Lemperle is the chief person in charge of IDEs for ventricular assist devices and total hearts. I have seen several applications that suffered because the sponsors were unwilling to keep in frequent touch with the agency and get their questions answered early in the trial or to cooperate with the agency so that major holes in the project can be patched early before eventually reaching panel review. Once you reach panel review, if there is missing information, it will hurt.

Let's go to the subject of selection criteria, which has been mentioned over and over in this two-day meeting. As a practicing physician who has used these devices, I have a slightly different view than some of the regulators in the agency. At the time I review these applications, I think I have a feeling for the physician's concerns at the time the decision is made to implant these devices. I do not entirely agree that selection criteria have to be rigidly enforced at the bedside. We all know the patient has only hours to live. We have to make a decision to implant the device and what to do. Although our inclusion and exclusion criteria are intended to stratify the study, there are going to be protocol deviations. There are going to be compassionate uses. My emphasis to the sponsors is to make sure that you are willing at all times to collect data on all these patients and subgroup them for analysis.

Just the same, you must identify a primary target group. That primary target group will eventually have to reach a number of subjects that is large enough for us to

analyze as a primary indication for the device. So, if there are significant numbers of protocol deviations, we will eventually start to wonder which is the primary target group. If there is an occasional compassionate use, those people fall out as outliers, and they are very easy to deal with at panel review if the target group is well studied.

Next, it is important to delineate and decide what the expected morbid complications are and define them. Definitions for these complications must be applied universally to all the patients across all the centers. If one person is calling something an apple and another person is calling it an orange, the statistics are not meaningful. The steering committee is of tremendous value in establishing not only the primary target group but also how morbid complications are defined. At the end of the analysis, I am going to look at those definitions and I expect that your incidence of complications reflects that definition. But if the definitions keep changing from center to center, I will question what the incidence of those complications really means.

In that respect, I have seen several studies in which the data collection forms and the methodology varied from center to center. That is a very bad practice, overall. Sponsors should insist that the principal investigators maintain common reporting methods as much as possible. If you are going to stratify or quantify events, if you are going to use a check form or an on-line computer database, everybody should follow the same reporting practices. Then we know what the data mean.

I think it is important that a sponsor takes a very close look at its potential study centers. This is a tremendous commitment, and the centers need to be able to provide the resources to capture the data up front. If they are interested in the device but they do not have the in-house personnel, if they do not have the commitment, or they have never done anything like this before, it is going to be hard to get this information back to the company on each and every one of these implants. And it will just make it harder to get to panel review. It is always sad to see a good device come to the panel with one center carrying two-thirds of the information, and the other centers have used it only a few times and there are no data. That really is not a multicenter trial.

I am rather biased in having direct physician input in follow-up and complication reporting. I think that one of the things I would like to see, which is not currently done in VAD protocols, is for the principal investigator to create a summary of the case for each patient. I have found a tremendous value in reading PMA applications when I actually get a summary of each case. There are often a lot of tabular data in PMAs. There are a lot of graphics generated from the sponsor's computer, but I want to know what happened at the bedside. And the best person is the principal investigator. Often they assign their study coordinator to fill out the check list, but I think the FDA should ask that the principal investigator dictate a summary of every case. What happened in the operating room? What happened in the intensive care unit? What led to the death of the patient? This is extremely hard to reconstruct from the patient's chart by a study coordinator

sent to the center two months later, and that decreases the value of that information.

I cannot over-emphasize the importance of autopsies. I have personally seen applications where the autopsy report has been valuable in establishing a patient-related complication and removing concern about device-related complications. We expect to see postmortem reports in the application so that we can see the wording ourselves. They are extremely valuable. Operative reports have equal value and should be copied and forwarded for every case. The same is important for critical radiographs. If you have a large series of left ventriculograms or multigated acquisition scans and you are looking for a significant difference, have them reviewed by an outside, independent, blinded interpreter. A simple report that the principal investigator says "this is an improved ejection fraction" may not be valid.

Explant analysis! I think this is an extremely important point. It is a unique opportunity to prove that your device is working, that it did not break, that it did not clot, and that it did not get infected. I want to encourage each sponsor to develop a standardized methodology for explant analysis that is common to each trial center. Insist that the device be sent back. Tell them how to do it. Provide them the equipment. In addition, I think the explant analysis should have a semiquantitative scoring system so that you can look at things such as sites of thrombi and extent of infections. Use a semiquantitative way of presenting these data to the panel.

Do not be shy in getting metallurgy, scanning electron microscopy, and other forms of failure analysis. Those types of things are very solid information when we want to know why the device broke. And if that problem was identified and fixed, it will be interpreted in your favor at panel review. Aggressively test any device that you or the investigator think has failed. For the same reasons, we want to know what happened, or what might have happened, to the patient if you pushed the device all the way to failure, and what those failure modes are. If a device is working outside of its normal range and you receive it back, test it to failure and make a full report so we know what happened. There is a chance that somebody on the panel will spot this problem and ask you how that device performed on the bench.

I would like to mention another issue about study centers. Sponsors should be willing to shut down centers that are misusing the device or habitually violate the protocol. We have seen such violation. It is very damaging to the final analysis of the study, and it does not do patients any good. I also believe that if the center is failing to capture the data, that is just going to hurt you during the subsequent PMA approval process.

Regarding the panel meeting itself, here are a few clues about what I like to see. Bring the device. You would be surprised how few people bring the device. There are some people who have never seen it and who are sitting on the panel about to decide whether you should market it. I think that there is something to the "seeing is believing" concept. Bring the investigators who have implemented the largest number of devices. These are

people who know about what is going on. They can answer questions by panel members regarding what the complications reported during the trial meant. If they have had problems, we want to talk to them and find out what their responses to those problems were. Do not forget to bring special consultants. You have in-house engineers, physical chemists, and hematologists who help you set up this program. You have quality control people who will be able to answer specific questions about the manufacturing of the device. Bring your grassroots people from the company. Bring your engineers and your study coordinators, because there just might be a key question that they can answer better than anybody else.

Prepare for questions by bringing your raw data. Bring tables. Some people have even brought portable computer databases. They are valuable. Bring photographs of your devices and explant analyses. Data that have been collected but are not brought to the meeting could be considered as damaging information that is purposely withheld. If you bring it, there is a good chance it may be favorably interpreted.

Here is one final word about labeling. Do not make sweeping statements or claims about how this device would work in everybody. Be specific. Do not try to advertise in the product literature. Such advertising is going to eventually be deleted anyway. The intended target group in the product labeling must match the PMA study group. Do not add a few extras on there so you can increase your potential market. We will restrict it to the group studied in the IDE.

It is important to illustrate and carefully explain to novice operators how to properly use the device. Rely on illustrations, and make sure that you put plenty of cautions and warnings for things that were detected during the clinical trial. Update that labeling for things that have been identified in the trial.

Now I will make one final comment about the panel itself. We receive a very large amount of documentation with only a few weeks to review it. Try to keep it organized. It is my preference that the agency limit the size of the submission to 50 pages or less. We have seen tremendous redundancy in these applications. Every other page restates the same thing, and often it restates claims of effectiveness. We will make up our minds if we think it is effective or not. So avoid too much advertising in the PMA, too many global claims of effectiveness, and boil it down because the reading burden is tremendous.

MODERATOR HILL: Thank you very much. That is a wonderful, practical summary of the whole process. Are there any questions right now directed toward it?

MR GLEN A. RAHMOELLER (Arlington, VA): Does the guidance that Ms Lemperle described in her presentation this afternoon reflect also the panel's views on what should be in the applications? That is, has the panel reviewed in detail the guidance that Ms Lemperle described?

DR LEVINSON: The guidance that I referred to is several years old. Ms Lemperle has summarized opinions

and decisions that have taken place inside the FDA, but I am not aware that they have been formally printed in the Federal Register. Is that correct?

MR RAHMOELLER: That was not my question. My question was, has the advisory committee reviewed the guidance that Ms Lemperle described? Is this a reflection also of the advisory committee's views on this subject, or is this something that has been developed within FDA without formal review by the advisory committee? That was the question.

DR LEVINSON: I am going to defer to Ms Lemperle. I have not seen this work inside the agency. I believe it is developed inside the agency.

MR RAHMOELLER: I think it is an important point because initially the advisory committees were set up to provide medical input to the agency, and in fact the medical device advisory committees until the most recent law differed from the drug advisory committees because the medical advice advisory committees were required to review applications—it was not at the FDA's discretion. From my input I think it is important to make sure that the physicians on the advisory committees have input to these types of guidance that are reflected in IDEs and deficiency letters that go to the industry.

MS LEMPERLE: When the guidance document was developed it was circulated to everybody, to our panel for their input, to industry for their input, and to all the physicians and all the committees. I have updated it to some degree in what I gave you today. But essentially it is the same thing that was put together early in 1988.

DR O. H. FRAZIER (Houston, TX): Who selects this panel, Dr Levinson? How is this panel arranged that you are on?

DR LEVINSON: I do not know who the individuals are who select the panel. It is done inside the agency itself. I was contacted by Bill Letsing at that time. He has left, and there have been a number of changes in personnel. But when there is a particular need, the devices division invites consultants who do not have an obvious conflict of interest financially with companies and who have experience in the area they need. Usually those individuals sit on one or two sessions, and if they are of the right level of experience they may be invited to sit as a voting member for subsequent meetings. Now Dr Abhijit Acharya is here and Dr Acharya has the central role in that section, so I might defer the rest to him.

DR ABHIJIT ACHARYA (Rockville, MD): The advisory panel members rotate on and off. Usually they serve about two to four years, so when there is a vacancy we publish it in the Federal Register asking for nominations from interested parties. We occasionally get nominations from professional societies and others. A lot of times we do not get any response at all from the Federal Register. I suspect

that you all do not read Federal Registers. I do not blame you. At that point, we use our informal contacts with physicians currently on the panel and physicians we know of from meetings and professional societies and request participation. Because the circulatory assist system panel has to be balanced between electrophysiologists, cardiologists, and cardiac surgeons, we do look for those specialties when a particular vacancy occurs with an eye to the proper balance.

SPEAKER: What is the number of people on the panel?

SPEAKER: It is seven working members plus there is an industry representative and a consumer representative.

SPEAKER: So it can be just nominated from the field, basically. It is not a professional.

DR FRAZIER: One thing that has concerned me for a long time is the inclusion for chronic heart failure patients of the acute failure circulatory data that Jack Norman generated in the 1970s. Probably 20% of our patients who are outpatients awaiting heart transplantation have cardiac indexes of less than $2 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$. And as I showed you today, I had three young people die in August who died of chronic heart failure. The oldest one was 44 years old without ever reaching these criteria. Do you know of any mechanism by which that criterion, which is inappropriate for this patient group but has hung on from the 1970s, can be changed?

SPEAKER: I was listening to the presentation of those patients and I had the exact same impression. From my particular perspective I felt those patients should have received implants and been treated as outliers in the analysis.

DR FRAZIER: Well, I cannot do that because I have already been informed by the FDA if I ever do that again I cannot do any more research in a field that I have worked in since 1964.

DR ACHARYA: I think in handling that the only particular way you can do that is to attempt to redefine those criteria and submit them as a protocol addendum. Virtually change the protocol. Because you have found that the inclusion criteria are too restrictive. You have patients who need the service who are otherwise candidates according to the 1991 viewpoint, and you have to amend the protocol. I am sure that discussion will be difficult, but that, I think, is the way it has to be handled.

DR FRAZIER: But to who? To where? I have been trying to hit it for years now, and I have been unsuccessful. So I do not know how to deal with it.

MS LEMPERLE: We have been in contact in the past with the circulatory committee. We have talked about admission criteria, and we are open to talking to them

again. We would be very happy to. We welcome discussion on this.

DR FRAZIER: Well, if we could get to the committee somehow, I think we have the data. But I am not sure exactly how to do that. But you would say to write some sort of addendum and the committee could investigate it, perhaps.

DR ACHARYA: Let me just throw this out. It is a suggestion. I think if you feel that these criteria are too restrictive and you are losing good-quality candidates, submit a protocol addendum and ask for it to be sent to the physician panel. I think that I would support personally expansion of criteria if the limitation you are having is cardiac index or blood pressure, because we have all seen patients who do not fit each and every single one of those but are still candidates for a device. If you feel that you can expand it and give it in some written format to us, I would be more than happy to review it and recommend to the agency that they expand that protocol.

DR FRAZIER: Thank you.

SPEAKER: Ms Lemperle, does this type of modification restart the clock on an application for a device? That is the sense that I get with the murmurings around the room; that while the doctors want to change the criteria the industrial people want to keep them the same so we can get them to market.

MS LEMPERLE: That is correct. If you are going to change the criteria you are going to change the study and it will mean new patients entering in the study, or expanding the study.

SPEAKER: That is a difficult catch-22.

DR FRAZIER: This is so even if you can show that the criteria are incorrect in 1991? Is that science? Because we can easily show that.

MS LEMPERLE: We would be delighted for you to present something that we could review.

DR FRAZIER: That is not science, and we all know that is not. This is absolutely crazy, this cardiac index thing.

MS LEMPERLE: I think you are trying to answer two different questions here. I think the second question that was brought up is, if the criteria are changed, does that restart the clock? And I suspect that it would restart the clock for that group of patients. The other group of patients, if they were large enough to be examined would be examined, and they would stand on their own. Is that correct?

DR ACHARYA: Yes. That is how I would look at the final submission. I think that if you change those criteria and you do it across all the centers in the study and they adhere to the new criteria, then you simply form a group

1 and a group 1A and they can fall out in analysis. You might have to go from 50 patients to 65 to get through, but I do not think you have to start at zero with a whole new study. That is one value in trying to get the physicians on the panel to look at these new criteria and see if they will basically approve these inclusion criteria and then analyze the group as a whole and then the two subgroups. Chances are that as you loosen up the criteria as you describe you are going to increase the number of patients and make the trial move along. I would still support this particular trial you are referring to with the expanded criteria. I do not think you have to start at ground zero for it.

DR FRAZIER: We can belabor this probably too much, but I am not talking about loosening up the criteria. I am talking about making the criteria medically and scientifically appropriate to the patient group we are studying or attempting to study. It is not a loosening up. It is just simply righting something that is off keel. I would not want it to be misinterpreted; in fact it might in some ways narrow the criteria. But it needs to be scientifically directed toward what causes death in the chronic heart failure patient awaiting a heart transplant, which is totally different than the patient with an acute myocardial infarction or the patient with failure to wean after cardiectomy. It is a different patient group. Whereas we have criteria that are for that patient group. I would not want to be viewed or to be thought of as supporting something just because we want to do more. I want to make it more focused in a scientific way toward the patient group that we are addressing.

DR ACHARYA: Let me summarize what I think I heard. First of all, if you are going to have entrance criteria and start a study group, the time to establish that is at the beginning. Correct? Second, I think that you have indicated that the FDA and the panels are receptive to rediscussing these entrance criteria for a defined group of patients whether they be myocardial recovery, bridge to transplantation, or permanent, that these could be rediscussed if they are properly outlined and presented back to the FDA and to the panel. Did I understand that right?

DR LEVINSON: They will be discussed. I think members of the panel feel that these protocol amendments are normal behavior as long as they are handled in a scientific fashion. I cannot speak for the regulatory people inside the agency. I will have to ask Ms Lemperle if she agrees.

DR ACHARYA: This has been a very sticky point over a long time. I think it does illustrate the difference between the physicians who practice, physicians who have run studies like this before, and the regulatory people. That is why this panel does exist.

MS LEMPERLE: I think it would take a lot of discussion to go over the issues, because I think Dr Frazier is referring to a study that has already had its protocol changed, and it is established the way it is now for a

specific reason. I think that if the protocol was changed again it would take a lot of thought and consideration between the sponsor and the FDA with his input and the input of other investigators in it. I certainly would not want to make a decision about that now. We would be willing to discuss it, but it would undoubtedly prolong the study.

DR ACHARYA: But as a matter of practice, if brand X came along and they had some sort of device that they wanted to introduce into a certain patient group, the entrance criteria for those group can be discussed and negotiated to be realistic for medicine for 1999—for 1991.

MS LEMPERLE: Yes. You could have a separate patient group that could be studied under the IDE. You would look at that group separately, while you are continuing to study the other group.

DR ACHARYA: That is what I mean. Or even an entirely new device. There are more devices in the minds of these people here, and they want to know that when the time comes to go out of their animal studies into humans the entrance criteria that they can work with possibly may not be the same historical ones that have existed, if it makes sense to change them.

MS LEMPERLE: That is correct.

MODERATOR HILL: I think we will move on, unless you have something else to add.

DR ACHARYA: There are trials that do not have historical inclusion and exclusion criteria. They have to be made up for that device as it enters the market. There are some devices that do not have history behind them and do not have the Norman criteria. So the sponsor has to generate those based on the medical indications he thinks are appropriate and the types of patients that he thinks he is going to serve, and firm those down. I think the FDA has always supported the sponsor defining those.

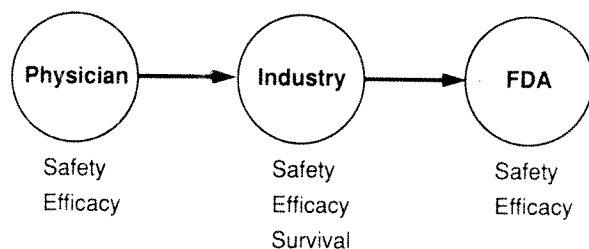
MODERATOR HILL: Well, we have heard from two of the advocates of society that are trying to support our patients, and now we will hear from another important one, industry. Victor Poirier is here from Thermo Cardio-systems to represent their point of view and their advocacy.

MR POIRIER: It takes the cooperative effort of three independent groups, all working together, to achieve success in making a life-saving technology available to a patient. As shown in Figure 1, each group shares in the common concern of patient safety, patient well-being, and device efficacy. Industry, however, has an additional concern, and that is survival—not the patients' survival, but the company's survival.

Industry is always positioned between the physician and the FDA. The physicians' primary concern is with the patients' well-being. It is their responsibility to address

CLINICAL STUDY

Patients' Well-being



TCI
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Fig 1. Three independent groups required for a study.

issues of patient care, patient selection, and study protocol. The industry's primary concern is how can it best carry out this study to satisfy FDA requirements while satisfying the physicians' primary concern of patient survival. This discussion addresses industry's concern about study protocol and FDA requirements and how these affect company survival.

Unlike the physician and the FDA, industry must be concerned with its survival. Several companies have come and gone in this field because of the difficulty in getting a device to market. This difficulty is not necessarily of a technical nature, but of a business nature. These difficulties reduce to a consumption of capital and the length of time that capital is at risk. The key is time. Changes in devices, changes in protocol, and delays in approval are all very damaging and can make the difference between life and death to a company.

Our own experience with the HeartMate assist device is a good example of the magnitude of the problem that industry must face. The initial concept of the HeartMate blood pump was in 1975. It took us 10 years, to 1985, before we had sufficient data to submit an application to the FDA for an IDE. After receiving approval, the study was initiated in 1986 and is ongoing. We have submitted our application for commercial approval and hope to receive approval in the very near future. The total time in this case is thus 17 years.

This time-consuming process is also expensive. This process has taken a minimum of 17 years at a cost of approximately \$25 million. This is not a concern with the FDA, nor is it with the physician. It is, however, a major concern for industry. The testing and development time is too long, the risk of investment is too high, the investment is too large, and the payback period is too long. It is clear that this technology would not exist without the initial support from the National Heart, Lung and Blood Institute. Delays can mean the difference between success and failure. Much is left to be learned regarding interfacing this technology to patients. Information is constantly evolving; we are constantly learning things that were not previously known to the FDA, the physician, and industry.

Working with a new technology presents many prob-

lems to all of us, and results in delays. We begin a clinical evaluation with a carefully selected protocol and learn about the device and its interaction with the patient during these early experiences. As a result, we change protocols and lose time. Every day lost and every patient who cannot be counted in the study can result in the failure of a company. Time for industry means expenses. Investors are not willing to wait for a return on their investment that is any longer than they could get elsewhere. Three to four years is as long as an investor is willing to wait. This is a serious problem that industry must face.

Because of the new technology, the FDA is continuously changing requirements and guidelines. There is a significant difference between the amount of data that were required to receive an IDE in 1985 and 1990. Not only were more data required, but the time to obtain the approval was also greater. In 1985, it took 5 months, whereas in 1990 it took 11 months to obtain the approval for a very similar device. How long will it take next time? How can industry schedule time and expenses to accomplish a task when requirements change all of the time?

Testing requirements that are imposed on industry can also be time-consuming and very costly. For example, is it reasonable to base the time that a device is approved for use in a human on animal test data? Animal testing is the most expensive and time-consuming element in the development process. Historically, it has been shown to be impractical to run a series of animals longer than 4 months. Because FDA requirements dictate that animal testing must be conducted to twice the intended duration of use, the longest approval time possible is 2 months. Our clinical experience shows that the average use in a patient is 3 months.

Animal experiments should be conducted to learn as much as possible about biological considerations. Extensive series of at least 8 animals over a specific period is of limited value in predicting clinical performance.

Can we also minimize the in vitro testing requirements before the start of a clinical study? Is it useful to do testing beyond what is necessary to demonstrate that the device is effective? Can in vitro testing be completed during the IDE phase after effectiveness has initially been demonstrated? Can in vitro testing be done in parallel with the clinical study?

Considering that the IDE phase is a continuation of the device testing, do we need to test everything that is required for a PMA before the IDE phase? Do we really need to test at least two times the intended duration at the worst-case conditions? One or the other should suffice, not both. If we do not test everything before the clinical trial, there is, of course, a small risk. Shouldn't the patient make the final decision as to what risk he or she is willing to take? What is the patient risk without the device?

Delays and modifications in devices or protocol are costly. It is expensive to monitor a clinical trial. In our case, to collect data and monitor the clinical study requires one director, two monitors, two data control persons, and part-time statisticians and analysis at a cost of \$500,000 per year, or \$42,000 per month. This is just to monitor the

program and does not include the cost of applications. Every month represents another \$42,000 expense.

Delays can be terminal—one month can make a significant difference to a company or an investor. Delays in adding new clinical sites, delays in approving protocol, and delays in reviewing reports can shake investor confidence and can mean the difference between success and failure of a company. Investor confidence is extremely important for a company.

In summary, industry's perspective is quite different from that of the FDA and the physician. Industry's survival depends on a timely and efficient approval process. Industry must know what the ground rules are and that they will stay firm.

Industry needs FDA guidelines. What are the performance standards? How can we reduce the "back and forth" with the FDA? Can we establish a standard protocol for each patient category?

How can we expedite these clinical studies? We need to have a mechanism to increase the number of study sites to broaden the breadth of our experience. We need to expedite patient entry into the study, and we need to reduce the *initial* in vitro testing requirements without jeopardizing the patient.

The FDA, like industry, must work within a budget. The FDA is underfunded and certainly understaffed. How can the FDA get through everything that is handed to it? The FDA has a tough job to do with limited funds. Industry has a tough job to do with limited funds. Working together is the only answer. We collectively need to be at least as good as our Japanese and German colleagues, who have already approved left VAD systems.

MODERATOR HILL: Do we have any questions from the floor? I think what I got from that is that you are calling for a change. Just for a point of discussion, do you have any specific things that if you had the ability to change you would? You covered the areas, but ultimately anything that is suggested, the test that it has to pass is that the device eventually goes into the patient with the highest knowledge that it is safe and effective—safe for sure; effectiveness maybe to be seen, or partly to be seen. Could you be specific about anything you would suggest to do?

MR POIRIER: Yes. I have been involved with this for many, many years, and we learn every year. We get new information. Certainly patient entry criteria is a hot subject. As Dr Frazier indicated, we established criteria in 1975 between Jack Norman and Bill Bernhard. The criteria are fine for postcardiotomy patients, but they are just not right for chronic congestive heart failure. If we had to start over we would look at different criteria. But at this stage of the game, after seven years into this study, how can we change? We really cannot. Every year that I look at this I have more and more requests for testing on these devices. And I really questioned that in the beginning under an IDE phase. To try to get an IDE phase, is it really necessary to measure time derivative of pressure in blood

pumps if in your animal studies you show that the plasma free hemoglobin level is less than 10 g/dL? Do we really have to do that test? Do we really have to test batteries at 0°C before we get an IDE when the patient is going to be in the hospital all the time? Those are very expensive, time-consuming data. Why can't we do that during the IDE phase? In parallel with the IDE, not before. It just goes on and on. There is a lot of testing that is required of us that is very time consuming and very expensive, and I just wonder when it should be done. It needs to be done before PMA, but maybe it is more appropriate to do it during the IDE phase than before the IDE phase.

MODERATOR HILL: I think everybody has experienced what you called back and forth. There are limited resources at the FDA, and as you know they are burdened with a lot of paperwork, and the industry is also burdened with a lot of things. How could that be tightened up and consolidated?

MR POIRIER: Communications. We need to talk more. The FDA has to understand what our problems are. We have to understand what their problems are. And we have to talk a lot more. I think that is the bottom line. If we understand where we are coming from then I think we can expedite things.

MODERATOR HILL: Are there any comments from the floor on this general area?

DR JOHN LAIRD (North Reading, MA): I wonder what there is for methods or channels of communication between industry and the FDA other than those that are specifically tied to a particular application and questions on procedures and so forth. We have heard about the physicians' position in the matter of the structural component of communication, but where does industry get to talk about the more general issues with the FDA?

MODERATOR HILL: What is the vehicle by which you could possibly bring about the change that has been suggested?

DR LAIRD: My own view is that industry is always in a delicate position. You do not want to raise questions that can somehow jeopardize a particular application you may be dealing with. But there are these very general questions, which have been already described. How can one communicate those? Or how can you get a discussion going about that problem?

MODERATOR HILL: Does the American Association of Medical Instrumentation (AAMI) get involved in this?

SPEAKER: Do they represent industry in this area with the FDA?

MS LEMPERLE: I can ask some of my colleagues if they want to comment on this also. But we do work with AAMI and with the Health Industry Manufacturers As-

Table 1. United Network for Organ Sharing Waiting List—Severity of Congestive Heart Failure (Jan 1990 to Dec 1990)^a

Status	No. of Patients	Died (%)	Received Transplant (%)	Average Wait (days)
I	1,046	295 (28.2)	658 (63)	54
II	1,426	231 (16)	710 (49.8)	303

^a As of October 31, 1991.

sociation (HIMA), and we do work informally with the manufacturers.

SPEAKER: It would be wonderful for me to see the FDA more involved out in the field and seeing these patients. I think it is extremely important to understand what this technology is, and I do not think you can understand what it is unless you really meet with the patients, talk with the patients, and see what their family life is all about. It is not only the patient who is having a tough time here. It is the family also. And as human beings I think we have to consider everything, not only the science but the patients' well-being as well. I would stress that the FDA should put in their budget some money so that they can go out in the field and see these patients and get involved with these patients. They should do a lot more than what is being done.

MODERATOR HILL: Industry in this case should get together and make some suggestions of how they could increase the efficiency; I think that is what we are looking for. This is best done through an official society trying to create a dialogue and to improve both industry's position and the FDA's without increasing the risk to the patient. Through a society, is that the best way to do it?

SPEAKER: We have worked before with the FDA and with the physicians. And I would think that the industry could work with AAMI or HIMA.

SPEAKER: I think it does not matter which group you work with. I think The Society of Thoracic Surgeons is obviously concerned about the physicians. Whether it is Hema or some other group, what has worked best in the past is if all of the manufacturers of a given type will get together and come up with some consensus; that can often have a big impact in dealing with the FDA because they are speaking with one voice.

MODERATOR HILL: We will now go on to the final advocate of the patient and hear from medicine's representative, Bartley Griffith from Pittsburgh.

DR GRIFFITH: My role today is to better define the current status of patients with morbid congestive heart failure so that the counter-poised risk and benefit of prosthetic hearts in the 1990s can be approached contemporarily based on a decade of past experience. In my pursuit of options for these patients, usually by way of cardiac transplantation, I am convinced of the benefits of

currently available "experimental" devices. In the real sense, no one is better able to judge than the patient's real advocate—responsible physicians who are clinical investigators. I believe that far too often patients are lost on the Scylla and Charybdis of rigid safety and efficacy statutory standards applied by nonclinicians, originally written as medical device amendments to the Food, Drug, and Cosmetic Act of 1976. Although the latter was a needed reaction to increasing complexity of devices and was ushered in due to shortcomings of intrauterine devices, pacemakers, and others, the current premarket approval or PMA requirements for ventricular assist devices and artificial hearts are perhaps outdated, and ignore the progress of the last decade in the clinical recognition of imminently lethal congestive heart failure and prosthetic ventricles. The paradox facing the design of experimental protocols for devices intended to treat serious and life-threatening conditions is tied to the Gordian knot uniting valid and ethical science. The more scientific validity of a protocol, the more unethical the design may become. Strict criteria for patient entry, usually coinciding with a prospective control group, provides desirable validity but is ethically unjustified for those excluded with no hope of survival without a medical device. Currently the FDA remains inflexible with regard to patient entry into IDEs, which means manufacturers must deny some patients entry or risk a prolonged and fiscally exhausting wait for PMA. The problem seems to be the malalignment of risk versus benefit of prosthetic ventricles for a population of patients who have fewer alternatives and less likelihood of survival than those patients with the most severe forms of malignancy. It is interesting to look at the FDA's response to the outcry for therapy for those with the eventually lethal human immunodeficiency virus infection. The retroviral drugs, AZT and DDI, went through NDA (the DRN sequent of PMA) expeditiously at 3½ and 6 months, respectively. Precipitate movement of these drugs was due to acquired immunodeficiency syndrome drug priority at the FDA. A similar emphasis should be placed on mechanical blood pumps shown to be effective and reasonably safe for those with severe congestive heart failure. Clinicians alone provide inadequate lobby to force a significant change.

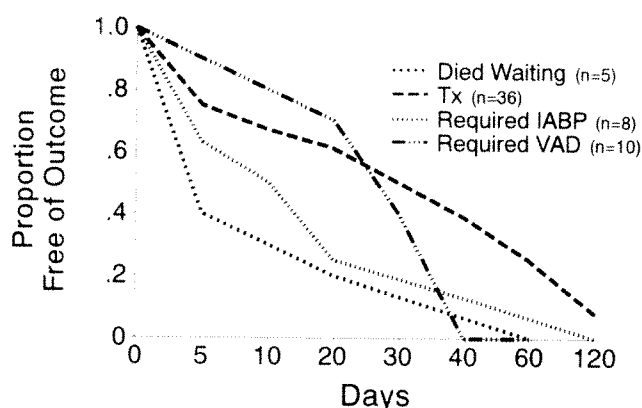


Fig 2. Outcome of 50 candidates dependent on inotropes (1/89 to 11/91). (IABP = intraaortic balloon pump; Tx = transplantation; VAD = ventricular assist device.)

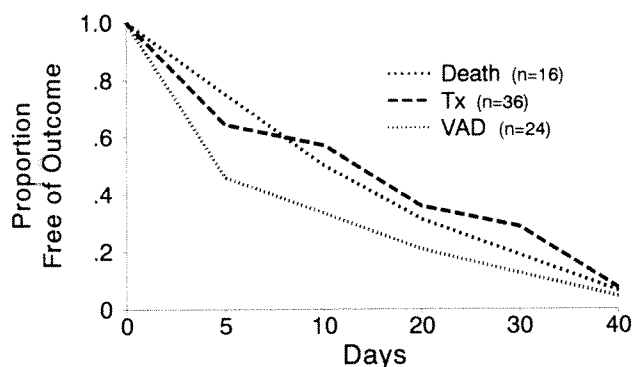


Fig 3. Likelihood of death, transplantation (Tx), or ventricular assist device (VAD) use in 54 intraaortic balloon pump-dependent transplantation candidates (1/89 to 11/91).

To better define the lethality of severe congestive heart failure, I have relied on the large United Network for Organ Sharing (UNOS) database, a snapshot of which in October 1991 showed that of 1,046 UNOS status I candidates listed for transplantation between January and December 1990, 295 or 28% died without a transplant. For those who received a transplant there was an average wait of 54 days. Of interest, a similar number, 231, but lower percentage, 16%, of status II patients died waiting for transplantation, which was performed on average at 303 days (Table 1). In Pittsburgh, 59 transplant candidates who were dependent on inotropes were followed up between January 1989 and November 1991. By three weeks approximately 50% of the inotrope-dependent candidates went on to have an event, 5 died waiting within 60 days, 36 underwent transplantation by 120 days, 8 required an intraaortic balloon pump by 3 months, and 10 needed a ventricular assist device within 40 days (Fig 2). Patients who depend on inotropes are clearly in unstable condition, and given a rather long wait for a donor, are more likely to advance toward lethality than to do otherwise.

A further evaluation of our candidates suggests that those dependent on an intraaortic balloon pump are at a high risk of death or requiring a ventricular device before

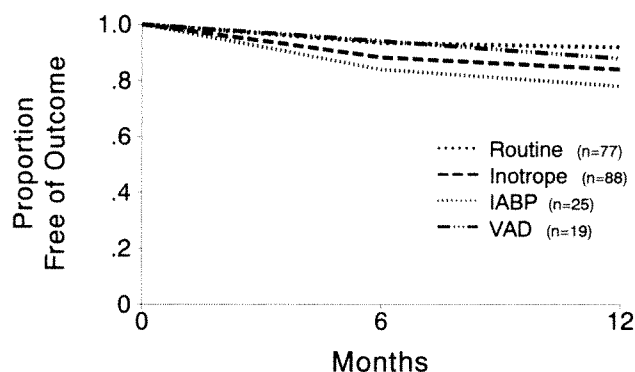


Fig 4. Survival after cardiac transplantation by candidate status (1/89 to 11/91). (IABP = intraaortic balloon pump; VAD = ventricular assist device.)

Table 2. Margin of Safety—Candidate Medical Status (Jan 1989 to Nov 1991)

Variable	Wait for Donor Heart			Time to Candidate Death		
	Mean (days)	Range (days)	n	Mean (days)	Range (days)	n
Status II	303 ^a			515		
Inotrope	50	0-325	36	20	1-74	5
IABP	21	0-74	14	16.5	0-46	16
VAD	73	2-144	10	75	5-303	5

^a United Network for Organ Sharing data.

IABP = intraaortic balloon pump; VAD = ventricular assist device.

transplantation (between 1989 and 1991). Sixteen of 54 intraaortic balloon pump-dependent candidates died by 40 days after implantation of the balloon, and most had succumbed before 3 weeks (Fig 3). Of those balloon-dependent candidates who received a ventricular device, most did so within a week. Data provided to me from Drs Frazier and Radovancevic of the Texas Heart Institute confirm the poor survival of intraaortic balloon pump-sustained candidates. The survival of 45 of their candidates averaged 25 days and ranged between 1 and 167. The tendency for our left VAD and routine candidates to have superior rates of survival (Fig 4) is also noted in major registries, including those of The International Society of Heart and Lung Transplantation and the Collaborative Transplant Trial of Opelitz. Combining UNOS data for status II patients with our data for patients who were placed on inotropes, intraaortic balloon pump, and VADs, one can clearly demonstrate the margin of safety or lethality of congestive heart failure (Table 2).

Well, what information do we have relative to the information on the safety of the available experimental VADs that are undergoing IDE scrutiny? Data provided from HeartMate, Novacor, and Thoratec suggest that death after implantation ranges between 35% and 41% and averages 38%. As previously mentioned, the rate of discharge after transplantation is superior to that obtained in patients not supported by a VAD and ranges between 77% and 93%, but averaged 86% (Table 3). Based on the data obtained from the Novacor and Thoratec series, the most common cause of death was multiple organ failure, which was responsible for 32% of those deaths (Table 4).

Table 3. Survival With Ventricular Assist Devices^a

Group	No. of Implant Deaths/ No. of Implants	No. of Hospital Discharges/ No. of Transplantations
Heartmate	18/44 (0.41)	20/26 (0.77)
Novacor	38/94 (0.40)	52/56 (0.93)
Thoratec	53/151 (0.35)	82/98 (0.84)
Total	109/289 (0.38)	154/180 (0.86)

^a Excludes current implants.

Table 4. Cause of Death

Group	Pretransplantation Deaths	Posttransplantation Deaths	
		Predischarge	Late
TAH	3/20: CNS (1), MOF (2)	8/17: mediastinitis (5), rejection (3)	2/9: CAD (1), N. Comp. (1)
Novacor	6/24: MOF (3), AMI (1), CVA (2)	0/18	2/18 CMV (1), rejection (1)
Thoratec	0/1	0/1	0/1

AMI = acute myocardial infarction; CAD = coronary artery disease; CMV = cytomegalovirus; CNS = central nervous system; CVA = cerebrovascular accident; MOF = multiorgan failure.

Other significant causes included bleeding, coagulation disorders, and sepsis. In our experience, these problems were related to advanced congestive heart failure and, thus, late selection. Although these devices pump blood well, they should not be intended for resuscitation heroics. If one wants to look very critically at potential device-related deaths, only right ventricular failure in the case of univentricular support, stroke, and intracerebral hemorrhage could be identified. Obviously, right ventricular failure is not a problem of the device, but again, a problem of patient selection. Not all strokes occur as a consequence of blood that is clotted within the prosthetic ventricle, as preexisting clots may exist within a dilated myocardium, and other intracerebral events usually occurring intraoperatively might, in fact, be based on technical error and not strictly device-related. The point, of course, is that no incidences of mechanical failure of the device have been recorded in any of the major series, and the causes of deaths almost uniformly select late or improper selection as the likely problem. To this end, restrictive protocols relative to patient entry seem to be more the problem than a protection for needy patients.

Finally, I believe something needs to be said relative to the clinical and human dynamic parameters necessary to redefine the most appropriate population to these devices that have already, in my opinion, demonstrated their safety and effectiveness. The initial Norman criteria published in the *Cardiovascular Disease TH1 Journal* in 1975 were left atrial pressures greater than 20 mm Hg, systolic blood pressure less than 80 mm Hg, or cardiac index less than $2.0 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ and an arteriovenous oxygen difference greater than 10 vol/%. These criteria were

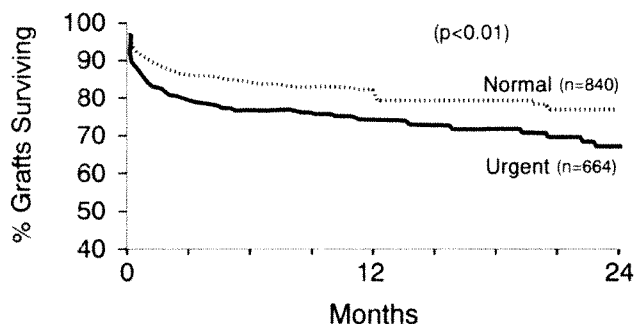


Fig 5. Survival after cardiac transplantation by medical status in a cooperative trial (G. Opelz, 1988-1990).

prepared for patients with acute illness as opposed to cardiac transplant candidates with progressive congestive heart failure. We evaluated a large number of our patients between 1989 and 1990 to determine if there were hemodynamic indices that might predict those who would die of sudden or progressive congestive heart failure. During that period, 37 patients survived to transplantation, 20 died with sudden death presumably with arrhythmia, and 18 died with progressive congestive heart failure. There were no significant differences in any of these three groups of patients in left atrial pressure, which averaged between 22 and 24 mm Hg, cardiac index, which ranged between 1.9 and $2.2 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$, or left ventricular ejection fraction, which ranged between 0.18 and 0.19. I believe that these data make it very difficult for strict reliance on hemodynamic parameters for protocol purposes relative to when a ventricular assist device should be implanted. So much of what we do as physicians involves experience and clinical judgement, which appears to be more valuable than the studied hemodynamic parameters upon which most of the protocols for patient entry criteria are based.

I believe strongly that, from a clinician's standpoint, morbid congestive heart failure represents a lethal disease and those afflicted are at a low risk relative to high benefit for the evaluation of these complicated devices. Ventricular assist device-related mortality is very low compared with problems encountered when patients are selected too late. The outcome of ventricular assist device bridging to transplantation compares with routine and appears better than that obtained for patients supported by inotropes and intraaortic balloon pumps. On behalf of the clinicians who are responsible for these patients, we plead, implore, and demand an appropriate redirection and alignment.

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Classified advertisements for positions wanted or available must relate only to the thoracic or cardiovascular surgical specialties. Display space (minimum, ¼ page) is also available through Art Carlucci, Elsevier Science Publishing, 655 Avenue of the Americas, New York, NY 10010 (telephone: (212) 633-3806; facsimile: (212) 633-3820). All advertisements are subject to the approval of the editor, and material deemed inappropriate for publication in *The Annals* will be rejected. If anonymity is desired, please indicate this at the time of submission and a code number will be assigned. All responses received will remain confidential in the publisher's office and will be conveyed to the advertiser shortly after receipt. The charge for all classified advertising is **\$1.60 per word per insertion, minimum 20 words**. Abbreviations, dates, initials, post office box numbers, telephone numbers, years, and zip codes are considered one word each. **There is an additional fee of \$25.00 per insertion for box number advertisements.** The copy deadline is 7 weeks prior to publication, eg, for the March issue, copy should be received by the 1st of January. Advertisement orders should be for a maximum of 6 months; advertisements may be renewed for up to 6 months at a time. Advertisement copy should be typed double-spaced and mailed in duplicate to: *The Annals of Thoracic Surgery*, Desk Editorial, Classified Advertisements, Elsevier Science Publishing Co, Inc, 655 Avenue of the Americas, New York, NY 10010 (facsimile: (212) 633-3853). Make *nonrefundable* check payable to Elsevier Science Publishing Co, Inc.

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SITUATIONS AVAILABLE

Thoracic and cardiovascular surgeon with emphasis on pediatric/neonate cardiac surgery and cardiac transplantation is needed by a full-service thoracic and cardiovascular surgery group on the west coast. Must have ABTS certification. Excellent salary and benefits package. Please respond with curriculum vitae and case list.

Please respond to Box 702. 702K/D

Cardiothoracic surgeon, board certified/eligible, wanted to join established practice in northwest Indiana (very near Chicago). Excellent salary. Please respond with curriculum vitae.

Please respond to Box 723. 723L/G

Board eligible or certified cardiovascular and thoracic surgeon needed to join a busy practice in the Southeast. Excellent salary and fringe benefits leading to partnership.

Please respond to Box 737. 737H/A

Cardiothoracic vascular surgeon, board certified or board eligible, to join well-established, busy one-man private practice in Midwest. Salary leading to partnership. Please send CV and references.

Please respond to Box 743. 743A/L

BC/BE cardiovascular and thoracic surgeon wanted to join busy two-member group in Fort Lauderdale, Florida. Recent US medical graduate preferred.

Please send CV to I. Tabry, MD, 2773 NE 37th Drive, Fort Lauderdale, FL 33308 ((305) 561-9781 after 9:00 PM). 746H/A

Cardiothoracic and vascular surgeon, board eligible or certified, to join 2-man private practice in Ft. Lauderdale, Florida.

Please send CV to Salem M. Habal, MD, 4800 NE 20th Terrace #107, Ft. Lauderdale, FL 33308; (305) 771-3220. 748H/A

Thoracic/cardiovascular surgeon: three-man group in suburban New York doing general thoracic and peripheral vascular surgery desires new graduate of approved thoracic program with training in vascular surgery. Please respond with CV.

Please respond to Box 758. 758I/B

Cardiovascular and thoracic surgeon: BE/BC wanted to join an established, busy private practice in the Midwest. Peripheral vascular expertise desirable. Recent graduate of a university program preferred. Salary leading to full partnership. Please respond with curriculum vitae and references.

Please respond to Box 763. 763I/B

Cardiothoracic surgeon—BE/BC—to join 2-man practice in South performing adult cardiac, thoracic, and vascular surgery. Surgeon finishing training or recent graduate preferred.

Please respond to Box 770. 770J/A

Cardiothoracic surgeon, BE/BC, to join busy 1-man private practice in mid-Michigan. Excellent opportunity. Salary leading to partnership. Please send CV and references.

Please respond to Box 779. 779J/C

Cardiothoracic surgeon needed to join established 2-man group in practice of adult cardiac, pulmonary, and vascular surgery. Must be board certified or eligible and graduate from a US medical school.

Please respond to R. W. Ruess, MD, 1834 Broadway, Cape Girardeau, MO 63701. 788K/A

Noncardiac thoracic surgeon wanted to join a group in northern New England. The practice would involve thoracic and general surgery. Must be board eligible or certified. Best in rural living. Please send CV.

Please respond to Box 791. 791K/A

Cardiothoracic and vascular surgeon urgently needed to join established practice in Midwest. Applicant must be BE/BC. Salary leading to full partnership. Please send CV and details of experience.

Please respond to Box 792. 792K/A

Thoracic and vascular surgeon, BE/BC, to join active (noncardiac) thoracic and vascular practice in central New Jersey. Please respond with curriculum vitae and details of experience. Salary leading to full partnership.

Please respond to Box 795. 795K/C

Cardiovascular and thoracic surgeon: Excellent opportunity for a board certified/eligible university-trained surgeon to join a new, growing department in a metropolitan New York community. Academic/private practice setting with excellent compensation. Experience in electrophysiologic surgery, artificial devices, and transplantation helpful. Please respond with curriculum vitae.

Please respond to Box 799. 799L/E

University of Florida seeks cardiovascular surgeon to join major teaching unit in Jacksonville, Florida, at University Medical Center. Candidate should be board eligible/certified in thoracic surgery. We seek someone with strong research and teaching interests. Position is tenure-acruing with academic appointment at Assistant to Associate Professor level, depending upon qualifications. Applicant recruiting deadline, April 1, 1993.

Forward curriculum vitae and names/addresses of three references to Eric Ceithaml, MD, Chairman, Cardiovascular Search Committee, University Medical Center, 655 W 8th St, Jacksonville, FL 32209. Affirmative action/equal employment opportunity employer. 801L/A

Cardiothoracic and vascular surgeon, board certified, board eligible to join an expanding three-man practice in the Rocky Mountain region. Please send CV and references.

Please respond to Box 802. 802L/E

Thoracic and vascular surgeon, BE/BC, wanted as associate/partner in private practice with clinical academic appointment in Providence, RI.

Please respond with CV and references to Albert K. Weyman, MD, 100 Highland Ave. Suite 304, Providence, RI 02906.

803L/A

South of Boston: Two experienced thoracic surgeons in very busy private practice offer employment and partnership opportunity for third. Ideal location 20 miles south of Boston offers educational and cultural advantages of an urban environment with options for country or suburban living. Excellent salary and benefit package, leading to full partnership. If BC/BE, please send CV.

Please respond to Box 805. 805L/E

General thoracic surgeon. The Massachusetts General Hospital and Harvard Medical School seek a highly qualified clinician, teacher, and scientist in general thoracic surgery. Training and experience in airway surgery and esophageal surgery required. Appointment would be at the rank of Instructor or Assistant Professor of Surgery at Harvard Medical School, depending upon qualifications.

Please reply with curriculum vitae and bibliography to Hermes C. Grillo, MD, Chief of General Thoracic Surgery, Massachusetts General Hospital, Boston, MA 02114. Harvard Medical School and Massachusetts General Hospital are affirmative action/equal opportunity employers. Women and minority candidates are encouraged to apply. 806L/B

The Division of Thoracic and Cardiovascular Surgery at the University of New Mexico School of Medicine in Albuquerque is seeking applications for a full-time faculty position at the Assistant/Associate Professor level for July 1993. We are looking for an individual with excellent skills in adult cardiac surgery and with specialized training in cardiac transplantation. The candidate must be board eligible or certified and have strong interest in research and teaching. This is an excellent opportunity for an individual interested in academic achievements as well as a good clinical experience.

Please forward curriculum vitae and three letters of recommendation to Jorge A. Wernly, MD, Chief, Division of Thoracic and Cardiovascular Surgery, University of New Mexico Medical Center-ACC2, Albuquerque, NM 87131. An affirmative action/equal opportunity employer. 809L/C

Cardiothoracic surgeon, board certified with 2 to 5 years experience. Wanted for practice in northeastern United States. Practice currently doing 500+ procedures and anticipates growth of 20%. Preferring surgeon with cardiac, thoracic, and vascular. Salary for 2 years, followed by full partnership. Please respond with CV.

Please respond to Box 810. 810L/A

Cardiothoracic/vascular surgeon: board certified in general surgery and BE/BC in thoracic surgery to join strong cardiovascular practice in western Pennsylvania. Major need for thoracic and vascular surgeon; cardiac surgery if desired. Excellent benefits. Detailed CV must accompany response. All replies treated confidentially.

Please respond to Box 811. 811L/E

Cardiothoracic surgeon, BE/BC, for Palm Beach County, Florida, busy, quality two-physician CVT practice.

CV to Kenneth M. Begelman, MD, 1599 NW 9th Ave, Boca Raton, FL 33486; FAX (407) 278-6887. 812L/A

Looking for a compatible cardiac thoracic surgeon with peripheral vascular experience and training. Ideal candidate would have training in electrophysiologic surgery. Southeast PA area. Early partnership offered to right candidate.

Please respond to Box 813. 813A

Cardiovascular thoracic surgeon—board certified/board eligible and recently trained to join an established, busy, dynamic and expanding private practice in northwest Indiana. The sphere of practice is approximately 30 minutes from downtown Chicago. Guaranteed excellent starting salary with progressive future growth and comprehensive corporate fringe benefit program leading to partnership for the right individual.

Write including CV and details of experience and capabilities to PO Box 3066, Munster, IN 46321. 814A/C

Cardiac surgeon to join established, two-man private practice in Chicago and its suburbs. Salary leading to full partnership. Excellent facilities and experienced associates.

If interested, please respond to Box 815. 815A/C

Emory University is seeking applicants for a faculty position in Cardiothoracic Surgery as Assistant Professor. Applicants should have demonstrated productivity in surgical research and be technically strong in all phases of adult and pediatric cardiac surgery as well as pediatric heart and lung transplantation.

Submit curriculum vitae and letters of recommendation to Robert A. Guyton, MD, Chief, Cardiothoracic Surgery, 1365 Clifton Road NE, Atlanta, GA 30322. Emory University is an affirmative action, equal opportunity employer. 816A

Experienced and board certified cardiothoracic surgeon needed to join an established group of thoracic and vascular surgeons in a newly approved cardiac surgery program in a community hospital. Responsibilities include coordinating and leading the cardiac surgical team of this group practice. Competitive package.

Please respond to Box 817. 817A/F

Cardio/thoracic surgeon: Exceptional opportunity for a cardiothoracic surgeon to join same.

Please respond to Allan O. Cook, MD, 4009 Worth St, Dallas, TX 75246; (214) 823-2103. 818A

Cardiovascular and thoracic surgeon, board eligible/board certified, to join a very busy, well-established and expanding private practice in Northeast with medical school affiliation. Excellent salary and benefits leading to partnership.

Please respond to Box 819. 819A

Director—Cardiothoracic Surgery: Board certified cardiac surgeon needed to coordinate and direct a new cardiac surgery program in a community hospital in association with an established group of surgeons. Strong community and medical staff support will assure a successful program. Attractive financial package.

Please respond to Box 820. 820A/F

Noncardiac thoracic and vascular surgeon, BE/BC, to join established one-man private practice on Florida's southeast Gold Coast. Send CV and details of experience.

Please respond to Box 822. 822A/C

Cardiothoracic surgeon: The University of Maryland, Department of Surgery, Division of Thoracic and Cardiovascular Surgery is seeking a cardiothoracic surgeon at the Assistant Professor level. Successful candidates should have training and expertise in cardiac transplantation, laboratory research experience, and a firm commitment to an academic career. Excellent fringe benefit package.

Please send a current curriculum vitae and three professional references to Joseph McLaughlin, MD, Professor and Head, Division of Thoracic and Cardiovascular Surgery, Department of Surgery, University of Maryland, c/o Lois Reisig, Department of Surgery, 5th Floor, 405 W Redwood St, Baltimore, MD 21201. EOE/M/F/H/V, minorities and females are encouraged to apply. 823A

Thoracic and vascular surgeon, BC/BE, needed for community practice in Northeast. No cardiac surgery. Please send CV.

Please respond to Box 824. 824A/B

Cardiothoracic and vascular surgeon to join a well-established three-man adult CV practice in California's Central Coast. Applicant must be BE/BC. Recent graduate of university program preferred. Please respond with CV.

Please respond to Box 825. 825A/B

Cardiovascular surgeon wanted to join three surgeons in an established adult cardiac, thoracic, and vascular surgery practice in north central Texas. Must be board certified/eligible. Salary plus benefits with full partnership available. Please send resume and references.

Please respond to Box 828. 828A/C

Junior or senior level position, thoracic and cardiovascular surgery: The Department of Surgery of the University of Wisconsin-Madison Medical School is recruiting a faculty member in the Division of Thoracic and Cardiovascular Surgery with an interest in a range of clinical, teaching, and research responsibilities. This position requires specialization in thoracic and cardiovascular surgery.

Applicants should submit resumes by January 30, 1992, to Robert M. Mentzer, MD, Chairman, Division of Thoracic and Cardiovascular Surgery, University of Wisconsin-Madison Medical School, Room H4/358 Clinical Science Center, 600 Highland Ave, Madison, WI 53792-3236. The University of Wisconsin is an affirmative action/equal opportunity employer. 831A

Faculty/academic position: The Division of Cardiothoracic Surgery, University of Washington, is seeking a BC/BE, adult cardiothoracic surgeon. The individual will have a dual appointment at University Medical Center and the Veterans Administration Medical Center. He/she will be responsible for continuing the VA clinical, educational, and research programs. He/she should have demonstrated a strong clinical cardiac surgery background and commitment to education and research. AA/EOE.

Send complete curriculum vitae to Edward D. Verrier, MD, Division of Cardiothoracic Surgery, RF-25, University of Washington, Seattle, WA 98195. 834A/B

General thoracic surgeon, BE/BC, wanted to join private practice at university-affiliated teaching hospital. Strong background in peripheral vascular surgery desirable. Location in Northeast suburban area. Excellent opportunity.

Send CV to Dr Charles Sills, Program Director, Monmouth Medical Center, 300 Second Ave, Long Branch, NJ 07740. 835A

Academic general thoracic surgeon: The Division of Cardiothoracic Surgery and the Section of Thoracic Surgery invites applications and nominations for a faculty position in general thoracic surgery at the University of Washington. Prospective candidates should be American Board of Thoracic Surgery eligible or qualified as of July 1, 1993, have demonstrated excellence in clinical surgery and research, and possess a commitment to teaching. Preference will be given to those who have broad experience in general thoracic surgery including lung transplantation. The successful candidate will be involved in the clinical programs at the University of Washington Medical Center, Harborview Medical Center, and Seattle Veterans Administration Hospital in Seattle as well as becoming actively involved in the Lung Transplant Program, the Cardiothoracic Surgery Laboratory, and in participating in the Thoracic Surgery clinical trials.

Applicants should have their curriculum vitae sent to the following address: Douglas E. Wood, MD, Chief, Section of Thoracic Surgery, University of Washington, Division of Cardiothoracic Surgery, SA-25, Seattle, WA 98195. University of Washington is an equal opportunity, affirmative action employer. 836A/B

SITUATIONS WANTED

General thoracic surgeon (BC), mature, looking for community with need, preferably Northeast or Southwest and group practice. Recent 10 years general surgical experience (BC) including laparoscopy.

Please respond to Box 741. 741H/A

Cardiothoracic surgeon, 35 years old, university trained, board certified with two years busy private practice experience. Seeks opportunity with new program, individual, or group in the Southeast.

Please respond to Box 757. 757J/C

General thoracic and general surgery combined. Board certified. Recent graduate looking for an exciting practice. Interest in endoscopic and laser surgery.

Please respond to Box 790. 790K/D

56-y.o. Thoracic and cardiovascular surgeon, American graduate, university trained, numerous publications, advanced surgical degree. Recent 3 + 6 months tutorial in vascular and general surgery. Wishes to relocate.

Please respond to Box 794. 794K/A

Cardiovascular and thoracic surgeon, ABS certified, ABTS eligible, currently at a major university center. Excellent training in all aspects of adult cardiovascular and thoracic surgery including heart and lung transplantation. Extensive prior experience in the specialty in England. Seeks opportunity with private or academic group practice. Available July 1993. CV and references upon request.

Please respond to Box 796. 796K/A

Cardiothoracic surgeon, ABS, ABTS eligible, desires position with busy cardiothoracic group. Can assist or operate, considerable thoracic and ICU experience.

(504) 868-9358. 800L/A

FELLOWSHIPS

Surgical residents/fellows—Clinical residency/fellowship positions available in adult and pediatric cardiothoracic surgery. Large volume of cases. New Jersey license required. Excellent salary and benefits.

Please contact Lynn B. McGrath, MD, Chairman, Department of Surgery, Deborah Heart and Lung Center, 200 Trenton Rd, Browns Mills, NJ 08015; (609) 893-6611, Ext 359. 653A

Fellowship in adult cardiac surgery beginning July 1993 and available for one or two years in private program performing over 600 open heart procedures yearly. Cardiac surgery training required. ECFMG and visa qualified foreign applicants accepted.

Send curriculum vitae to Donald R. Kahn, MD, 817 Princeton Ave, Suite 300, Birmingham, AL 35211. 786K/A

Fellowship in a very busy pediatric cardiovascular surgery center is available July 1993. Experience includes performing surgery for very complex congenital heart disease and participation in ongoing educational and research activities. Illinois license or equivalent required. Salary and benefits exceed \$45,000.

Please respond to the Division of Pediatric Cardiac Surgery, The Heart Institute for Children/Christ Hospital and Medical Center, 4440 West 95th St, Oak Lawn, IL 60453. 821A/B

Cardiovascular surgical fellow: Department of Cardiovascular Surgery, San Francisco Kaiser-Permanente Medical Center, offers a one-year clinical fellowship in cardiovascular surgery beginning July 1, 1993. Applicants must be ABS BC/BE. High volume, excellent salary and benefits.

Please send CV and direct questions to M. Terry McEnany, MD, Chief, Department of Cardiovascular Surgery, Kaiser-Permanente Medical Center, 2350 Geary Blvd, San Francisco, CA 94115; (415) 202-3800. 826A/D

Cardiothoracic surgical fellowship—Allegheny General Hospital is seeking qualified candidates for a one-year, nonaccredited fellowship position in cardiothoracic surgery, available July 1, 1993, through June 30, 1994. The program enjoys a large volume of adult cardiac surgery and thoracic surgery cases, including thoracoscopy, esophageal and pulmonary resections, in addition to a strong research program. The program is assisted by seven physician assistants.

Please send a CV and letters of recommendation to George J. Magovern, MD, Professor and Chairman of Surgery, Allegheny General Hospital and the Allegheny Campus of the Medical College of Pennsylvania, 320 E North Ave, Pittsburgh, PA 15212. 827A/D

Cardiothoracic surgical fellowship. Available July 1, 1993, to June 30, 1994. One year noncredited appointment available to persons completing general surgery residency to assist in the

preop management, surgery, and postop management of cardiothoracic surgical patients.

Submit complete curriculum vitae to John C. Baldwin, MD, Professor and Chief, Cardiothoracic Surgery, Yale University School of Medicine, 333 Cedar St, PO Box 3333, New Haven, CT 06510. Yale University is an affirmative action/equal opportunity employer. 829A

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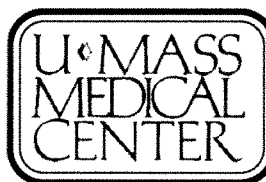
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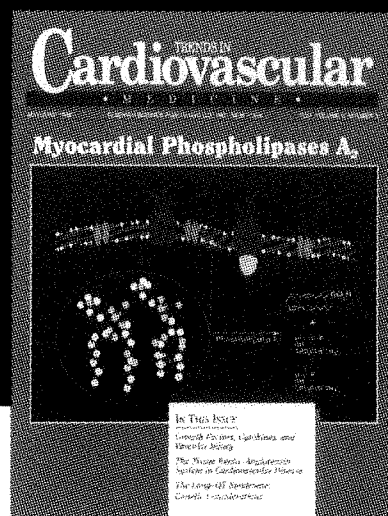
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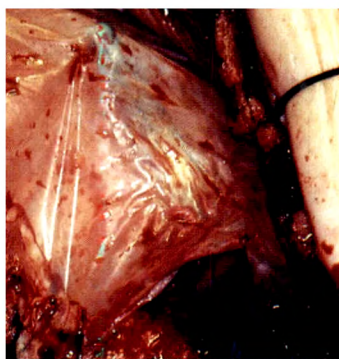
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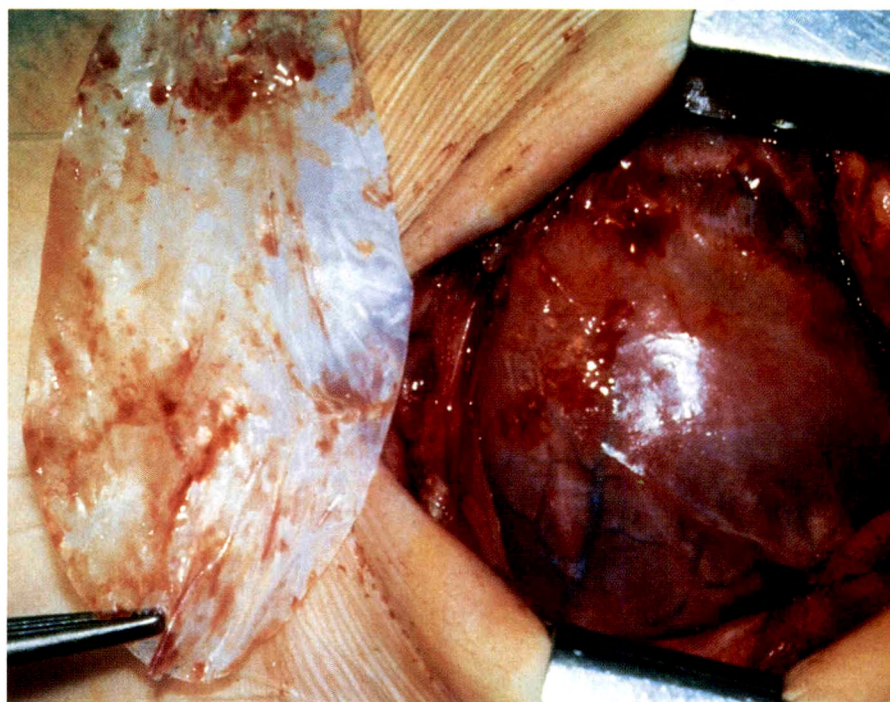
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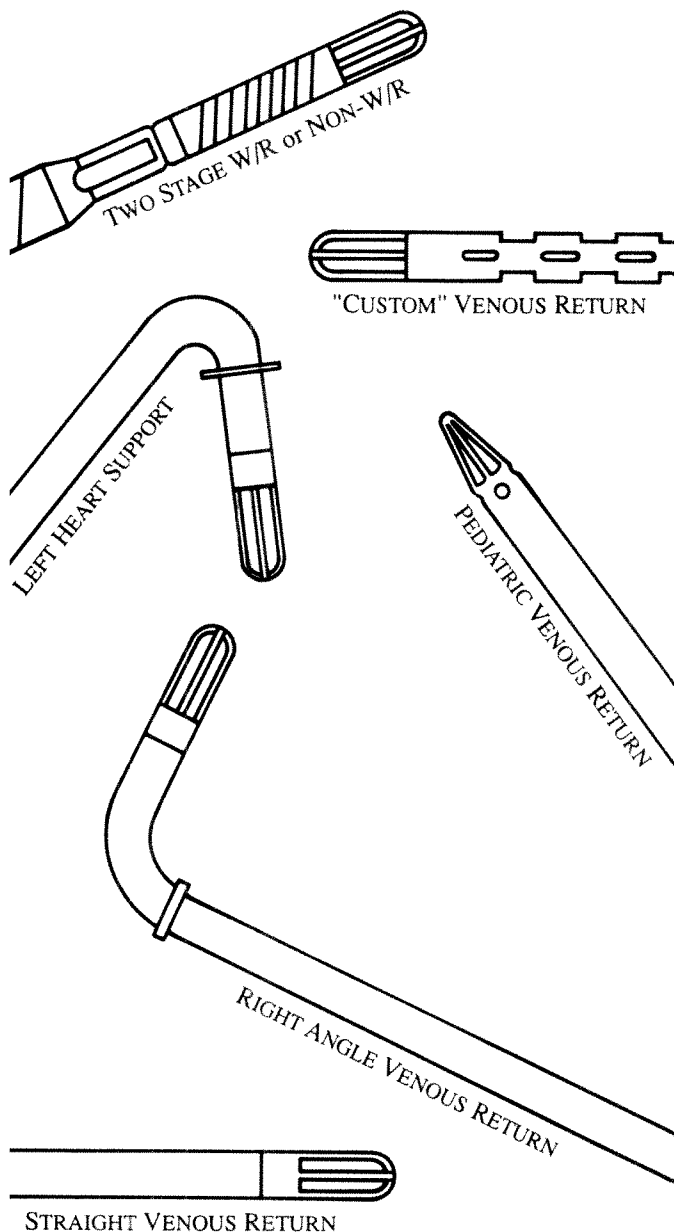
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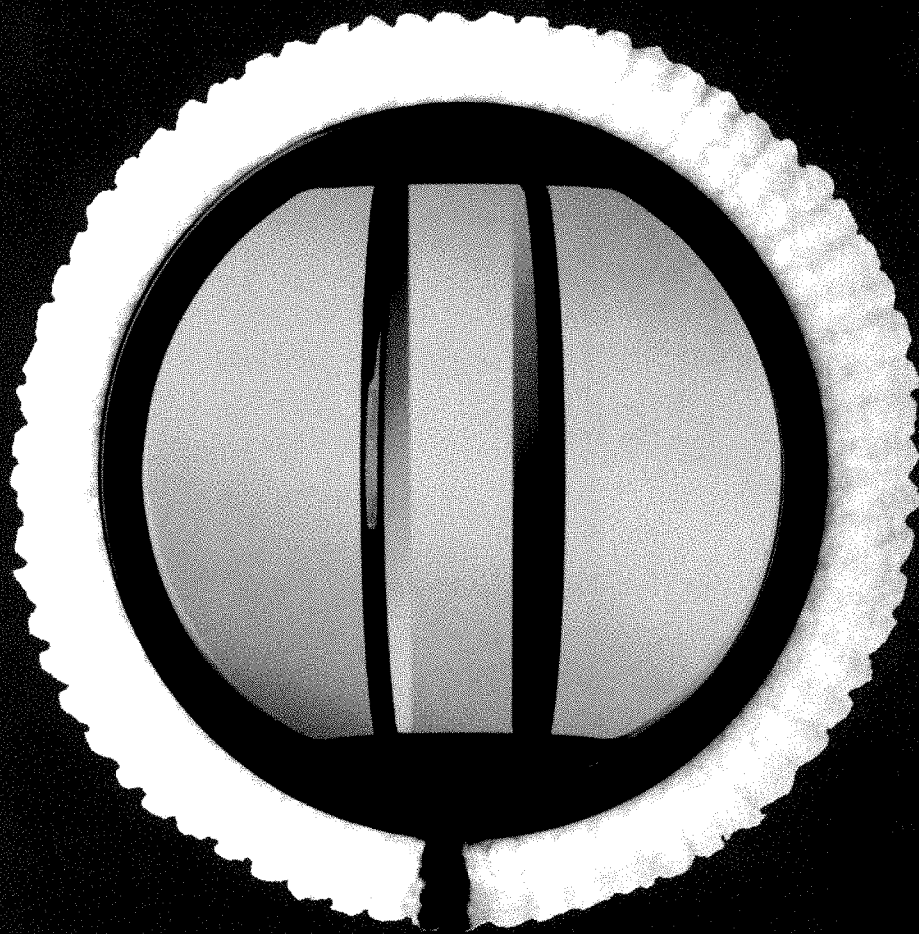
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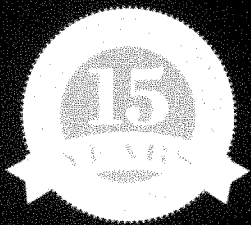
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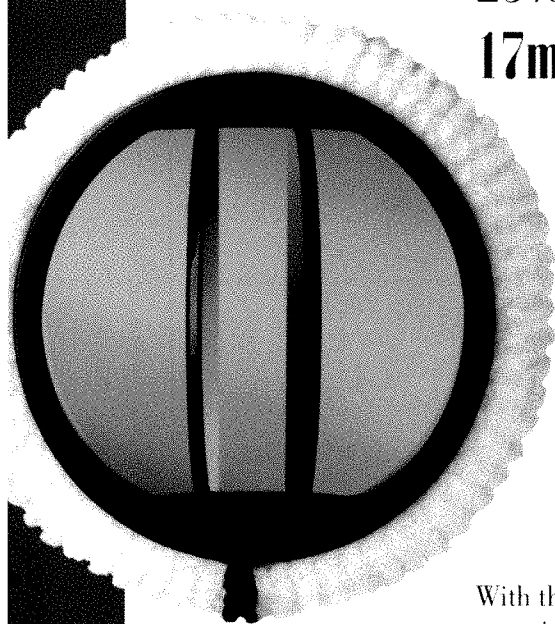
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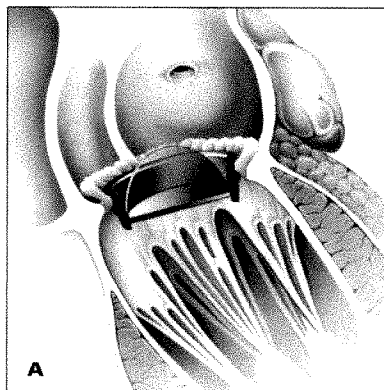
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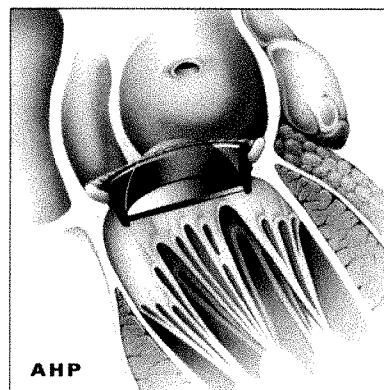
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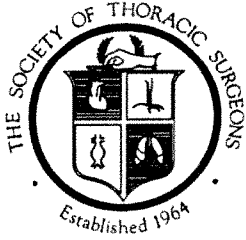
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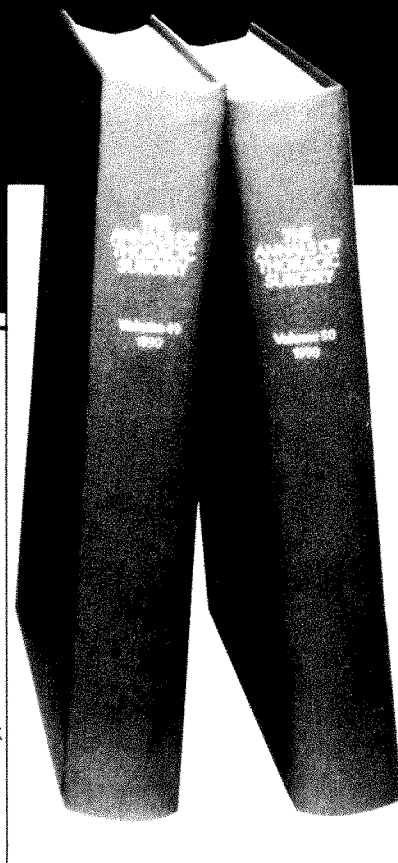
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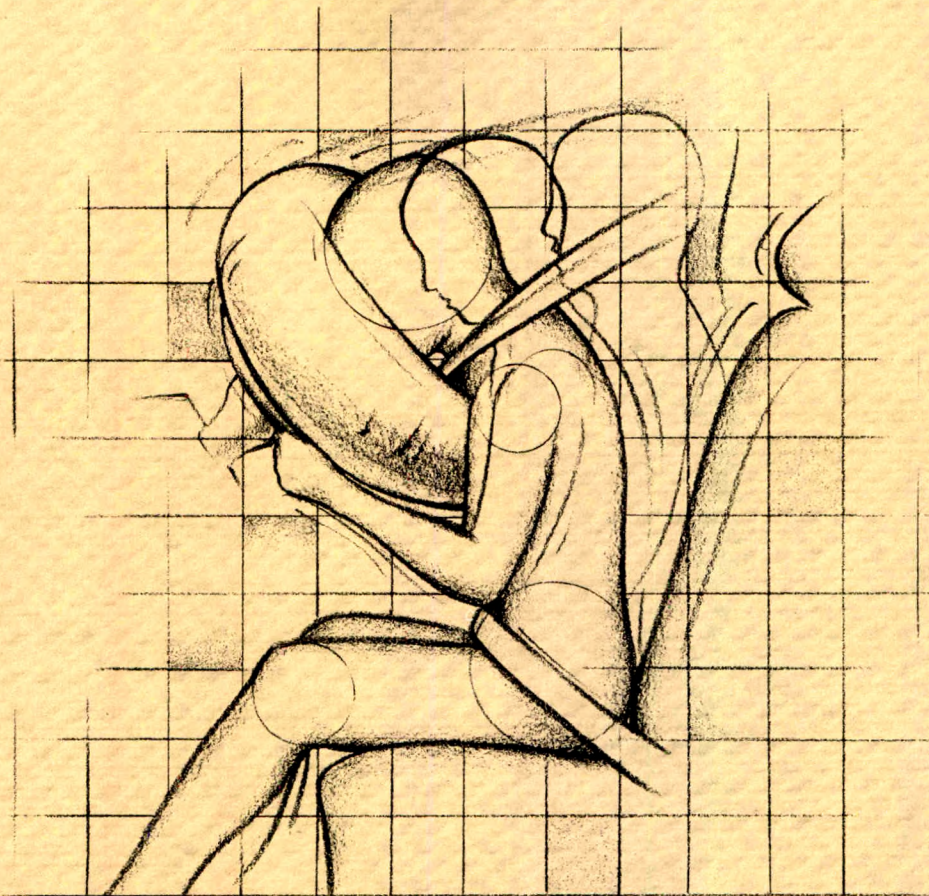
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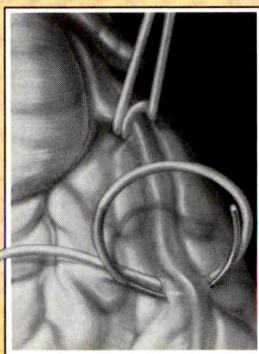
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- 2) All design considerations for typefaces, page layout, and artwork will be handled by the publisher after receipt of the electronic manuscript. **There is no need for the author to input special typesetting codes.**
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EVENTS OF INTEREST

Brief notices of meetings, courses, and symposia relevant to cardiothoracic surgery are published as a service. They should be formatted as follows: meeting title, date, place, sponsor, accreditation, director, fee, minimum/maximum attendance, and address/phone for further information. Announcements should be sent at least 4 months in advance of publication to *The Annals of Thoracic Surgery*, 3108 Queeny Tower, Barnes Hospital Plaza, St. Louis, MO 63110-1041; telephone, (314) 361-6084.

■ **Second Loma Linda International Conference on Pediatric Heart Transplantation, Rancho Mirage, California—March 10-12, 1993**

For information on this meeting, contact Leonard Bailey, MD, Loma Linda International Heart Institute, Loma Linda University Medical Center, Loma Linda, CA 92354; or telephone (800) INTL-HEART.

■ **Forty-second Annual Meeting of the American College of Cardiology, Anaheim, California—March 14-18, 1993**

For information on this meeting, contact American College of Cardiology, 9111 Old Georgetown Rd, Bethesda, MD 20814; or telephone (800) 253-4636.

■ **Neurohumoral Effects of Profound Hypothermia in Infant Heart Surgery, London, England—March 18-19, 1993**

For information on this meeting, contact The Postgraduate Centre, National Heart and Lung Institute, Dovehouse St, London SW3 6LY, England; or telephone 071-351 8172 (facsimile: 071-376 3442).

■ **Thromboembolic and Primary Pulmonary Vascular Disease: Diagnosis and Management, San Diego, California—March 26-28, 1993**

For information on this meeting, contact Pulmonary Vascular Disease

Conference, Shirley Kolkey, Conference Coordinator, 9606 Tierra Grande, #106, San Diego, CA 92126; or telephone (619) 271-6673.

■ **Le Club Mitrale, Paris, France—March 27-April 3, 1993**

For information on this live teleconference, contact Margo Irr, ProMedica International, 620 Newport Center Dr, Suite 575, Newport Beach, CA 92660; or telephone (714) 640-5870, extension 28 (facsimile: (714) 759-6911).

■ **General Thoracic Surgery: Surgery of the Esophagus, Boston, Massachusetts—March 29-30, 1993**

For information on this postgraduate course, contact Department of Continuing Education, Harvard Medical School, PO Box 825, Boston, MA 02117; or telephone (617) 432-1526 (facsimile: (617) 432-1562).

■ **One Hundred Thirteenth Annual Meeting of the American Surgical Association, Baltimore, Maryland—April 1-3, 1993**

For information on this meeting, contact American Surgical Association, Department of Surgery, CB 7245, University of North Carolina, 136 Burnett-Womack Building, Chapel Hill, NC 27599; or telephone (919) 966-4320 (facsimile: (919) 966-6009).

■ **Thirteenth Annual Meeting of the International Society for Heart and Lung Transplantation, Boca Raton, Florida—April 1-3, 1993**

For information on this meeting, contact ISHLT Headquarters, 435 Michigan Ave, Suite 1717, Chicago, IL 60611; or telephone (312) 644-0828.

■ **American College of Surgeons, Montreal, Canada—April 25-28, 1993**

For information on this meeting, contact American College of Surgeons, 55 E Erie St, Chicago, IL 60611; or telephone (312) 664-4050 (facsimile: (312) 440-7014).

■ **Seventy-third Annual Meeting of the American Association for Thoracic Surgery, Chicago, Illinois—April 26-28, 1993**

For information on this meeting, contact American Association for Thoracic Surgery, 13 Elm St, Manchester, MA 01944; or telephone (508) 526-8330 (facsimile: (508) 526-4018).

■ **Fourteenth Annual Scientific Session of the North American Society of Pacing and Electrophysiology, San Diego, California—May 6-8, 1993**

For information on this meeting, contact NASPE, 377 Elliot St, Newton Upper Falls, MA 02164; or telephone (617) 244-7300 (facsimile: (617) 244-3920).

■ **1993 World Symposium on Cardiomyoplasty and Biomechanical Assist, Paris, France—May 24-26, 1993**

For information on this meeting, contact Beverly Farrier, ProMedica International, 620 Newport Center Dr, Suite 575, Newport Beach, CA 92660; or telephone (714) 640-5870, extension 22 (facsimile: (714) 759-6911).

■ **International Symposium—Update in Cardiac Surgery, Coimbra, Portugal—May 28-29, 1993**

For information on this meeting, contact Prof M. Antunes, Cirurgia

Cardiotoracica, Hospital da Universidade, 3000 Coimbra, Portugal; or send facsimile to 351-39-29674.

■ **The International Society for Cardiovascular Surgery/The Society for Vascular Surgery, Washington, DC—June 7-9, 1993**

For information on this meeting, contact the Association offices, 13 Elm St, Manchester, MA 01944; or telephone (508) 526-8330 (facsimile: (508) 526-4018).

■ **Fifth European Congress on Extra-Corporeal Circulation Technology, Arles, France—June 9-12, 1993**

For information on this meeting, contact MOBO Promotions/FECECT, Catharijnesingel 105, 3511 GV Utrecht, Netherlands; or telephone 31-(0)30-310751 (facsimile: 31-(0)30-311198).

■ **World Congress on Diseases of the Chest, Amsterdam, the Netherlands—June 13-18, 1993**

For information on this meeting, contact XVII World Congress on Diseases of the Chest, International Academy of Chest Physicians & Surgeons, 3300 Dundee Rd, Northbrook, IL 60062-2348.

■ **Nineteenth Annual Meeting of The Western Thoracic Surgical Association, Carlsbad, California—June 24-26, 1993**

For information on this meeting, contact The Western Thoracic Surgical Association, 13 Elm St, Manchester, MA 01944; or telephone (508) 526-8330 (facsimile: (508) 526-4018).

■ **Le Club Mitrale, Paris, France—June 26-June 3, 1993**

For information on this live teleconference, contact Margo Irr, ProMed-

ica International, 620 Newport Center Dr, Suite 575, Newport Beach, CA 92660; or telephone (714) 640-5870, ext 28 (facsimile: (714) 759-6911).

■ **Ninth Congress of the International Society for Artificial Organs, Amsterdam, The Netherlands—July 4-8, 1993**

For information on this meeting, contact Congress Secretariat ISAO, RAI Organisatie Bureau Amsterdam bv, 1078 GZ Amsterdam, Europaplein 12, The Netherlands; or send facsimile to 31-20-6464469.

■ **Twenty-first World Congress of The International Society for Cardiovascular Surgery, Lisbon, Portugal—September 12-15, 1993**

For information on this meeting, contact ISCVS XXIst World Congress, Congress Secretariat, 13 Elm St, Manchester, MA 01944.

■ **Seventh Annual Meeting of The European Association for Cardio-Thoracic Surgery, Barcelona, Spain—September 20-22, 1993**

For information on this meeting, contact EACTS Executive Secretariat, Le Fugon, PO Box 51, rue Cardinal Richaud, F-33028 Bordeaux, France; or telephone 33 56 50 67 36 (facsimile: 33 56 50 67 43).

■ **Neurological Injury and Pediatric Cardiac Surgery (including results of the prospective Boston Circulatory Arrest Study), Boston, Massachusetts—September 30-October 2, 1993**

For information on this meeting, contact Laura Young, Department of Cardiac Surgery, Children's Hospi-

tal, 300 Longwood Ave, Boston, MA 02115; or telephone (617) 735-7930 (facsimile: (617) 735-6742).

■ **Fifty-ninth Annual Scientific Assembly, American College of Chest Physicians, Orlando, Florida—October 24-28, 1993**

For information on this meeting, contact American College of Chest Physicians, 3300 Dundee Rd, Northbrook, IL 60062; or telephone (708) 498-1400 (facsimile: (708) 498-5460).

■ **Fortieth Annual Meeting of the Southern Thoracic Surgical Association, Panama City Beach, Florida—November 4-6, 1993**

For information on this meeting, contact Southern Thoracic Surgical Association, 401 N Michigan Ave, Chicago, IL 60611-4267; or telephone (312) 644-6610 (facsimile: (312) 321-6869).

■ **Sixty-sixth Scientific Session of the American Heart Association, Atlanta, Georgia—November 8-11, 1993**

For information on this meeting, contact American Heart Association, 7320 Greenville Ave, Dallas, TX 75231; or telephone (214) 373-6300 (facsimile: (214) 373-3406).

■ **Thirtieth Annual Meeting of The Society of Thoracic Surgeons, New Orleans, Louisiana—January 31-February 2, 1994**

For information on this meeting, contact Richard P. Anderson, MD, The Society of Thoracic Surgeons, 401 N Michigan Ave, Chicago, IL 60611; or telephone (312) 644-6610 (facsimile: (312) 527-6635).

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■ Cox/Maze Procedure for Atrial Septal Defect With Atrial Fibrillation: Management Strategies

Lawrence I. Bonchek, MD, Mark W. Burlingame, MD, Seth J. Worley, MD, Brad E. Vazales, MD, and Edward F. Lundy, MD, PhD

■ DNA Ploidy Pattern of Each Carcinomatous Component in Adenosquamous Lung Carcinoma

Yukito Ichinose, MD, Nobuyuki Hara, MD, Shinzo Takamori, MD, Kazunobu Maeda, MD, Tokujiro Yano, MD, and Mitsuo Ohta, MD

■ Effects of Aprotinin on Anticoagulant Monitoring: Implications in Cardiovascular Surgery

David Najman, MD, Jeanine M. Walenga, PhD, Jawed Fareed, PhD, and Roque Pifarré, MD

■ Open Mitral Commissurotomy: Fourteen- to Eighteen-Year Follow-up Clinical Study

Jose M. Herrera, MD, Jose L. Vega, MD, Jose M. Bernal, MD, Jose M. Rabasa, MD, and Jose M. Revuelta, MD

■ Platelet Function in Cardiac Operations: Influence of Temperature and Aprotinin

Joachim Boldt, MD, Christoph Knothe, MD, Bernfried Zickmann, MD, Bill Sabine, Friedhelm Dapper, MD, and Gunter Hempelmann, MD

■ Primary Repair of Iatrogenic Thoracic Esophageal Perforation and Boerhaave's Syndrome

Sunil K. Ohri, FRCS, Theodore A. Liakakos, MD, Vivek Pathi, FRCS,

Edward R. Townsend, FRCS, and S. William Fountain, FRCS

■ Relation Between Choice of Prostheses and Late Outcome in Double-Valve Replacement

Paul S. Brown, Jr, MD, Charles S. Roberts, MD, Charles L. McIntosh, MD, PhD, Julie A. Swain, MD, and Richard E. Clark, MD

■ Surgical Experience With Defibrillator Implantation Using Nonthoracotomy Leads

Dieter Hammel, MD, Michael Block, MD, Wolfgang Konertz, MD, Martin Borggreffe, MD, Frank Isbruch, MD, Boulos Asfour, MD, Armin Geiger, MD, Günter Breithardt, MD, FESC, and Hans H. Scheld, MD, FICA

■ Third-Time Coronary Artery Bypass Grafting: Mid-Term Results

Walter H. Merrill, MD, C. Craig Elkins, MD, James R. Stewart, MD, William H. Frist, MD, and Harvey W. Bender, Jr, MD

■ Tracheoesophageal Fistulas

Leonid M. Gudovsky, MD, Nataly S. Koroleva, MD, Yury B. Biryukov, MD, Alex F. Chernousov, MD, and Mikhail I. Perelman, MD

Case Reports

■ Intraoperative Transthoracic Ultrasonographic Localization of Occult Lung Lesions

Hani Shennib, MD, and Patrice Bret, MD

■ Successful Combined Operation for Mitral Stenosis and Atrial Fibrillation

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MD, Takashi Nitta, MD, Atsushi Harada, MD, Tetsuo Asano, MD, Shigeo Tanaka, MD, and Tasuku Shoji, MD

How to Do It

■ Localized Supravalvar Aortic Stenosis: A New Technique for Repair

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■ Technique of Transplantation for Hypoplastic Left Heart Syndrome With Left Superior Vena Cava

Thomas L. Spray, MD, Charles B. Huddleston, MD, and Charles E. Canter, MD

■ Transseptal Insertion of Left Atrial Line: A Simple and Safe Technique

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Classics in Thoracic Surgery

■ Quantum Leap Forward in the Management of Cardiac Trauma: The Pioneering Work of Dwight E. Harken

Panagiotis N. Symbas, MD, and Alexander G. Justicz, MD

Current Review

■ Technical Advances in the Treatment of Left Ventricular Aneurysm

Noel L. Mills, MD, Charles T. Everson, MD, and David R. Hockmuth, MD

Is Coronary Reoperation Without the Pump an Advantage?

Delos M. Cosgrove III, MD

Department of Thoracic and Cardiovascular Surgery, The Cleveland Clinic Foundation, Cleveland, Ohio

Coronary artery reoperation is a mushrooming problem. By 1955 it is estimated that 55,000 patients will undergo coronary reoperations annually in the United States. Reoperative procedures have several technical obstacles that differentiate them from primary procedures. These problems include (1) difficulties with reentry, (2) potential for cardiac and conduit injury during dissection, (3) availability of conduit, (4) management of patent vein grafts, (5) myocardial protection, and (6) bleeding and blood use. In this issue of *The Annals*, Fanning and associates [1] present an alternative approach to reoperative coronary revascularization that eliminates the use of cardiopulmonary bypass. To evaluate the efficacy of this approach, it is necessary to analyze the advantages and disadvantages of this technique and how they relate to the specific problems associated with reoperative myocardial revascularization.

See also page 486.

This technique does not address, eliminate, or reduce the first four of these technical problems. Myocardial protection is simplified but not necessarily improved by elimination of aortic occlusion. Reoperation without the use of cardiopulmonary bypass has a potential advantage for reduction in bleeding secondary to the avoidance of the damaging hematologic influence of cardiopulmonary bypass. With significant improvements in the present-day cardiopulmonary bypass circuit, there are less damaging hematologic effects and it is now less of a problem than previously. New techniques such as intraoperative blood salvage and reinfusion of shed mediastinal blood have reduced the need for homologous blood. In our most recent series of patients undergoing reoperative myocardial revascularization using cardiopulmonary bypass at The Cleveland Clinic, the mean transfusion requirement was 2 units [2].

Electing not to use cardiopulmonary bypass and performing limited procedures that do not replace all grafts increases the potential for two recognized problems. First, manipulation of the heart without interrupting previously placed vein grafts increases the potential for embolization of atherosclerotic debris from old vein grafts. Angiography underestimates the extent and magnitude of the

atherosclerotic process in old vein grafts, making the potential for this complication unpredictable. This complication was noted in Fanning and associates' series, directly causing one of the deaths. Leaving old, patent, and not obviously stenotic vein grafts in place not only exposes the patient to the risk of embolization from under-diagnosed atherosclerotic disease but runs the risk of having the grafts become stenotic in the early postoperative period. This problem was also noted in Fanning and associates series, leading to reoperation.

The avoidance of cardiopulmonary bypass has not proved to reduce the overall mortality. In this series of 54 highly selected patients, the operative mortality rate was 3.4%. In 1,500 consecutive patients operated on at The Cleveland Clinic from 1967 to 1984, the operative mortality was 3.4% [2].

It is clear this procedure is not universally applicable. Fanning and associates recommend its use only for patients who have isolated circumflex disease or for patients with isolated right main or left anterior descending disease or a combination of the two. It is not applicable to patients who require grafting of the posterior descending branch of the right coronary artery or in patients who have vessels less than 2 mm in diameter. This substantially restricts the applicability of this approach to a relatively small percentage of the reoperative population. Fanning and associates employed this technique in 59 of 599 (10%) of their patients.

In summary, avoiding cardiopulmonary bypass may decrease the potential for bleeding and blood requirements in a selected group of patients but fails to substantially improve operative mortality or provide solutions to technical problems related to reoperative coronary artery bypass grafting. It exposes the patients to the risk of thromboembolic events from atherosclerotic vein grafts and early restenosis of untreated vein grafts. Reduction in bleeding complications is an attractive advantage, but the early and long-term risks associated with this approach do not weigh in favor of its widespread implementation.

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1. Fanning WJ, Kakos GS, Williams TE Jr. Reoperative coronary artery bypass grafting without cardiopulmonary bypass. *Ann Thorac Surg* 1993;55:486-9.
2. Lytle BW, Loop FD, Cosgrove DM, et al. Fifteen hundred coronary reoperations. *J Thorac Cardiovasc Surg* 1987;93:847-59.

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Warm Blood Cardioplegia: Back to Square One

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It appears that the latest fashion on the block is warm blood cardioplegia. That modality of intraoperative myocardial protection is being reported by several surgeons, and clinical acceptance appears to be growing [1–3]. Perhaps it will become the method of choice.

From my viewpoint, however, there remains a skeptical reminder that the history of “new” concepts is often a reincarnation of something old, forgotten, and discarded. Sometimes, of course, a rerun turns out to be surprisingly valuable because someone recognizes or stumbles upon the reason that a seemingly good concept failed and corrects the defect to achieve success. Such was the case with potassium cardioplegia introduced by Dennis Melrose in the late 1950s [4, 5]. His important contribution was initially heralded as a technical bonanza, only to be soon abandoned because of myocardial damage resulting from the high potassium concentration of his solution. It took cardiac surgeons more than a decade to recognize and accept the virtues of potassium cardioplegia at safe lower concentrations. This method of myocardial protection was combined with cardiac cooling and resulted in dramatic reduction of cardiac surgical mortality [6].

Seldom has a new and seemingly heretical modality become so rapidly and universally adopted. Within 2 years of its introduction more than 160 papers on the subject appeared in the English-speaking literature, *none* of which were derogatory or critical of the method and all of which offered some adjunct or reformulation to improve the already gratifying results.

Despite the evidence of effective protection from serious myocardial damage after long periods of aortic cross-clamping there was understandable discomfort about the method's imposition of prolonged ischemia; thus it was not long before oxygenated blood cardioplegia was promoted as an “improvement” on asanguineous crystalloid infusion [7]. More recently this reversionary measure has been augmented by also eliminating hypothermic protection and returning to normal temperatures of the infusate. In light of the history of cardioplegia, one is forced to wonder whether this is an improvement or a step backwards.

The literature is replete with a wide variety of approaches to protect the ischemic myocardium. There are multiple formulas for the infusate—both with and without blood, various patterns of intermittent or constant perfusion, and alternate directions of flow (antegrade or retrograde) [8]. Each proponent provides experience and data to suggest superior performance of one method over another. It is notable, however, that these comparisons,

occasionally of mathematical significance in single parameters, are largely trivial in contrast to the dramatic reduction in operative mortality that accompanied the introduction of simple asanguineous hypothermic potassium cardioplegia. The possible major exception to that statement relates to those patients with acute myocardial infarction [9].

Reversions to abandoned practices may be motivated by dissatisfaction with current methods or may merely be the product of “new” exploration by an “explorer” who is innocent of the reasons why that practice was dropped. The concept of keeping the heart perfused—and nonischemic—under near-normal conditions is appealing and could turn out to be a net benefit. However, it is important to remember that before the era of hypothermic (ischemic) cardioplegia the universally accepted method of myocardial protection was antegrade coronary perfusion with blood from the pump-oxygenator. This logical modality was nevertheless abandoned with alacrity because of its small but distressing incidence of universally fatal “stone heart.”

Three questions arise from this sequence of events: (1) Does myocardial perfusion with warm blood supplemented by cardioplegic solution—whether constant or intermittent—carry the same risks as similar perfusion with just warm blood from the pump-oxygenator without arresting cardiac function? Does “stone heart” continue to be a threat, or is it effectively prevented by the potassium relaxation? (2) Does the growing popularity of this normothermic modality arise from unsatisfactory protection with hypothermic cardioplegia? And, if so, is that dissatisfaction the result of a correctable technical inadequacy? (3) Does hypothermia really have sufficient detrimental effect to justify abandoning its safety and convenience benefits?

The implied or expressed rationale for the “warm” approach is a contention that hypothermia is detrimental to myocardial function, but I am unable to identify evidence of any significant harmful effect either in my clinical experience or the literature. It would seem, therefore, that there is no sound rationale for warm cardioplegia—even if it can be conducted with as much safety as hypothermic cardioplegia.

Buckberg [10], who has been the most voluble proponent of blood cardioplegia, presents evidence that the role of hypothermia in protecting the ischemic myocardium is less important than generally thought, and he elaborates at length on the metabolic factors that are potentially more important. He denigrates the time, expense, and effort associated with cooling the heart but *does not* demonstrate that it is harmful.

Modest concentrations of potassium render the myo-

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cardium inactive, and their protective effect is supplemented by hypothermia to an extent that permits long periods of ischemia with demonstrated safety. Imperfections in performance of that technique may be attributable to potassium wash-out by the collateral circulation or to rewarming by both collateral circulation and ambient heat sources. I have noted that these factors are frequently overlooked, which is a possible explanation for suboptimal results. It does, however, hardly make sense to abandon a safe and effective modality only because it is not being used properly.

The temperature gradient between the cold heart and both the surgical ambience and adjacent tissues (particularly the thoracic aorta) can be significantly reduced with (1) the adjunctive use of total body hypothermia, (2) elimination of the heat from overhead operating lights and use of fiberoptic headlights, and (3) covering of the exposed surface of the heart with cold pads or an insulating jacket. Body hypothermia has the supplemental benefit of permitting the pump to be slowed, which lowers pressure, reduces collateral flow, and diminishes oxygenator trauma to the blood. In addition it provides the handy option of stopping the pump (arresting the circulation) with great safety in the event of a power failure, mechanical problem, or just a technical desirability for a bloodless operative field. Although not a common occurrence, there have been several unanticipated episodes in which I have been gratified to use circulatory arrest with safety and comfort.

That safety feature, of course, is dependent on complete and uniform cardiac hypothermia, which can be achieved only with sufficient heat transfer to a volume of cardioplegic solution that is adequate to cool that particular myocardial mass to the desired temperature. A cardioplegic flush with 200 to 300 mL of a refrigerated solution—particularly if it has been standing for some time at room temperature—will effectively paralyze mus-

cular activity but will not provide complete uniform cooling of a 400-g adult heart. Heat exchange objectives should be calculated and a sufficient volume of perfusate should be provided to achieve the cooling objective.

Hypothermia has been a useful modality since the beginnings of open heart surgery. It has served cardiac surgeons and their patients long and well. Let us not be too hasty about abandoning it.

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Making Some sENSE Out of Thoracoscopy

Robert B. Wagner, MD

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Editor's Note:

The following represents a departure in form from the usual editorial comment. In his cover letter, however, Dr Wagner states, "I am fully aware that this manuscript is not in the usual scientific form which you publish in *The Annals of Thoracic Surgery*, but I am very serious about the content."

Another advance in the surgical science,
Has been heralded to us with much reliance,
That through several little holes placed hence and thence,
We may remove all pathology without morbid consequence.

We have applied the procedure with diligence,
To avoid complications with undue frequency,
For not to "keep up" would be impudence,
And forgo any chance of obtaining preeminence.

We use the scope in pleural disease with confidence,
With the lung collapsed it is our preference,
One can abrade, biopsy, and talc dispense,
This procedure really makes a lot of sense.

Lung biopsies and wedges may be done with little violence,
To chest wall muscles lying in residence,
Allowing patients to return to their own home thence,
And quickly to their jobs is the inference.

But to apply it to everything in the chest lacks intelligence,
And forsakes our surgical heritage which we learned as residents,
That good exposure makes for less accidents,
Which is of utmost importance for the patients.

Can one really safely perform resections whence,
Fissures are incomplete and adhesions dense?
It will be a while until there is any evidence,
That keyhole surgery won't lead to more local recurrence.

For fluid intrapericardial lying in residence,
Thoroscopic removal has been touted with grandiloquence.
Can we ignore the simplicity and excellence,
Of the subxyphoid route with benefits immense?

Should local thymic enucleations commence?
Does wide excision really make no difference,
Or are we not reverting to spreading incense,
And forgetting lessons learned from experience?

Esophageal surgery is unforgiving and of great consequence,
Of mistakes made even with exposure of wide circumference,
Should surgery, like Everest—"Because it is there" be condensed,
Or should overextensions of keyholes be considered as negligence?

There is no question of the video's magnificence,
And like TV, it can be sold to a wide audience,
If properly applied it can even cut down on expense,
But it shouldn't be done for the recompense.

Address reprint requests to Dr Wagner, 50 W Edmonston Dr, Rockville, MD 20852.

Valvular Disease in the Elderly: Influence on Surgical Results

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Aortic valve disease in the elderly is primarily calcific stenosis with preservation of left ventricular function. In contrast, mitral valve disease in the elderly often is ischemic in nature with damage occurring to both valve and myocardium. The present study was undertaken to compare results of aortic (AVR) and mitral valve replacement (MVR) in the elderly and to ascertain predictors of poor outcome. Because patients who had concomitant coronary artery bypass grafting (CABG) are included (51% for AVR, 55% for MVR), patients who had isolated CABG were used as a comparison group. Between January 1, 1984, and June 30, 1991, 1,386 patients aged 70 years and older underwent CABG ($n = 1,043$), AVR ($n = 245$), or MVR ($n = 98$). The operative mortality rates were 5.3% for AVR, 20.4% for MVR, and 5.8% for CABG. Late follow-up of patients undergoing operation in 1984 and 1985 was available for 98% (231/237). Overall survival was comparable for all three groups through the first 5 years of follow-up (AVR, $68\% \pm 8\%$; MVR, $73\% \pm 8\%$; CABG, $78\% \pm 3\%$). After 5 years, survival for patients having AVR and MVR was less than that for those having CABG. Patient age, sex, New York Heart Association functional class, concomitant CABG, prosthetic

valve type, native valve pathology, and preoperative catheterization data were examined as possible predictors of outcome by multivariate logistic regression. Among MVR patients, New York Heart Association functional class, ischemic valvular pathology, and higher pulmonary capillary wedge pressure were predictive of operative mortality; poor left ventricular function was a predictor of poor long-term survival (17% versus 100% at 7 years; $p < 0.0005$). Among AVR patients, only advanced functional class was associated with a poor outcome. Compared with MVR patients, AVR patients were older (76.5 ± 4.6 versus 74.5 ± 3 years; $p = 0.0002$), were more often male (55% versus 39%; $p = 0.006$), had a lower pulmonary capillary wedge pressure (18 ± 11 versus 24 ± 10 mm Hg; $p = 0.0001$), and had fewer critically diseased vessels ($p = 0.001$). These results suggest that AVR in the elderly has an operative mortality similar to that of isolated CABG. In contrast, MVR is less well tolerated, especially in patients with ischemic mitral disease. Survival 5 years postoperatively is similar among AVR, MVR, and CABG patients but becomes significantly worse thereafter for AVR and MVR patients.

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One of the most important recent developments in cardiac surgery over the past decade has been the marked increase in the number of elderly patients referred for open heart procedures. At our institution, we have witnessed an increase in mean age of patients undergoing isolated coronary artery bypass grafting (CABG) from 59.7 years in 1984 to 64.2 years in 1990.

Many elderly patients have cardiac valvular lesions that necessitate valve replacement. Aortic valve disease in the elderly is primarily calcific stenosis with preservation of left ventricular function (LVF). In contrast, mitral valve lesions in the elderly are often complex ischemic lesions. Persistent or repeated episodes of ischemia often result in chronic myocardial damage and dysfunction.

This report presents the experience at our institution with valvular operations in elderly patients. By examining mortality rates and risk factors predictive of a poor outcome for aortic (AVR) or mitral valve replacement (MVR), we have attempted to describe the influence of valvular disease on surgical outcome in the elderly.

Material and Methods

This study reviews the data for patients aged 70 years or older who underwent AVR or MVR between January 1, 1984, and June 30, 1991, at The Johns Hopkins Hospital. Because patients who had concomitant CABG are included, elderly patients who had isolated CABG were used as a comparison group. Patients who had multiple-valve replacements are excluded from this report.

Operative Technique

The surgical approach was through a median sternotomy. Extracorporeal perfusion was employed using bubble (earlier years of study) or membrane oxygenators with moderate systemic hypothermia (core temperature, 28° to

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30°C). The method of myocardial protection was single-dose cold (4°C) crystalloid hyperkalemic cardioplegia injected into the aortic root after placement of the aortic cross-clamp and continuous topical cooling with cold saline solution. Perfusion flow rates were maintained between 1.8 and $2.8 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ with mean arterial pressure between 50 and 70 mm Hg. A pulmonary artery vent was routinely employed.

Data Acquisition

Data were obtained by retrospective review of medical records, catheterization and pathology reports, death certificates, and autopsy reports. Data collected from medical records included New York Heart Association (NYHA) functional class, surgical status (elective versus urgent/emergent), and number of postoperative hospital days. Catheterization data consisted of LVEF, pulmonary capillary wedge pressure, number of critically diseased vessels ($\geq 70\%$ narrowing of the luminal diameter), trans-valvular gradient, valve area, and degree of regurgitation (graded angiographically from 1 to 4+). Operative reports provided the surgical procedure, valve prosthesis, and gross valvular pathology. Additional description of valvular pathology was obtained from formal pathology reports. Death certificates and autopsy reports provided dates and causes of death.

Follow-up Data

Follow-up information was obtained on patients who underwent operation in 1984 and 1985. Telephone contact was made with the patient, a family member, or the patient's current physician.

Statistical Analysis

Univariate analysis of potential risk factors for early mortality was performed using χ^2 analysis for discrete variables and unpaired t tests and analysis of variance for continuous variables. To determine independent predictors of mortality, variables with a p value of less than 0.1 in the univariate analysis were entered as covariates in a multivariate logistic regression model that contained age and sex (SAS Institute Inc, Cary, NC).

Factors possibly predictive of long-term survival were examined individually by Kaplan-Meier actuarial analysis, and their significance was determined by the Breslow test (BMDP Statistical Software, Los Angeles, CA).

All values are expressed as the mean $\pm$ one standard deviation except survival data, for which the standard error is reported. A p value of less than 0.05 was considered significant.

Results

The study population consisted of 1,386 patients: 245 underwent AVR, 98 underwent MVR, and 1,043 had isolated CABG. One hundred twenty-five (51%) of the patients who had AVR and 54 (55%) of the patients who had MVR had concomitant CABG. There were 135 men (55%) and 110 women (45%) in the AVR group, 38 men (39%) and 60 women (61%) in the MVR group, and 665 men (64%) and 378 women (36%) in the CABG group.

Table 1. Summary of Patient Data^a

Variable	AVR (n = 245)	MVR (n = 98)
Demographics		
Men	135 (55)	38 (39)
Women	110 (45)	60 (61)
Age (y)	76.5 ± 4.6	74.5 ± 3
Age range (y)	70-90	70-84
NYHA class		
I/II	11 (4)	2 (2)
III/IV	234 (96)	96 (98)
Status		
Elective	160 (65)	56 (57)
Urgent/emergent	85 (35)	42 (43)
Hemodynamics		
LVEF		
Poor	39 (16)	11 (11)
Fair/good	206 (84)	87 (89)
PCWP (mm Hg)	18 ± 11	24 ± 10
Valve gradient (mm Hg) ^b	65 ± 25	...
Valve area (cm ²) ^b	0.6 ± 0.2	...
Angiography		
0-Vessel disease	114 (47)	34 (35)
1-Vessel disease	60 (24)	19 (19)
2-Vessel disease	32 (13)	10 (10)
3-Vessel disease	39 (16)	35 (36)

^a Numbers in parentheses are percentages. ^b Data are for patients with pure aortic stenosis only.

AVR = aortic valve replacement; LVEF = left ventricular function; MVR = mitral valve replacement; NYHA = New York Heart Association; PCWP = pulmonary capillary wedge pressure.

Clinical, hemodynamic, and angiographic characteristics of patients having valve replacement are summarized in Table 1. Bioprostheses were used in 193 AVRs (79%) and 66 MVRs (67%). Five (three AVRs, two MVRs) were Ionescu-Shiley bovine valves; all others were Carpentier-Edwards porcine valves. All mechanical prostheses were St. Jude Medical valves except for one Medtronic valve in the AVR group.

Native valve pathology is detailed in Table 2. Pure aortic stenosis accounted for 208 (85%) of all aortic valve

Table 2. Valvular Pathology^a

Variable	Aortic (n = 245)	Mitral (n = 98)
Pure stenosis	208 (85)	16 (16)
Pure regurgitation	19 (8)	61 (62)
Mixed stenosis and regurgitation	18 (7)	21 (22)
Calcific	210 (86)	4 (4)
Ischemic	0 (0)	30 (31)
Rheumatic	6 (2)	35 (36)
Degenerative	5 (2)	17 (17)
Endocarditis	7 (3)	5 (5)
Other	17 (7)	7 (7)

^a Numbers in parentheses are percentages.

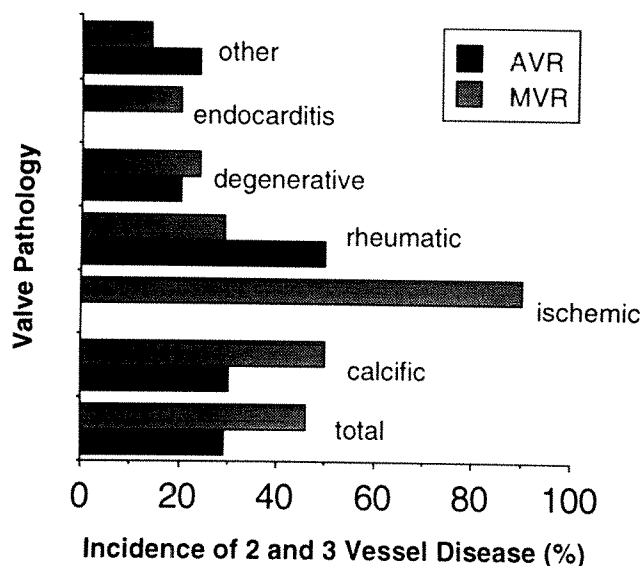


Fig 1. Incidence of two- and three-vessel disease according to valvular pathology. (AVR = aortic valve replacement; MVR = mitral valve replacement.)

lesions. One hundred ninety-nine (96%) of these 208 lesions were calcific in nature. Pure mitral regurgitation occurred in 61 patients (62%). Among all patients having MVR, rheumatic disease was suspected in 35 patients (36%). Ischemic lesions were the second most prevalent lesion, occurring in 30 patients (31%).

Figure 1 shows the incidence of severe two- and three-vessel coronary artery disease (CAD) in AVR and MVR patients according to valvular pathology. Only 29% (71/245) of AVR patients and no more than 50% of any pathological subgroup had disease of two vessels or more. In contrast, 46% (45/98) of MVR patients had severe CAD. The incidence was highest in patients with ischemic pathology (90%; 27/30).

The median number of days spent in the hospital postoperatively was 11 for AVR and 14 for MVR.

The 30-day mortality rate was 3.3% (8/245) for AVR and 14.3% (14/98) for MVR. In comparison, similarly aged patients undergoing CABG had a mortality rate of 4.7% (49/1,043). The in-hospital mortality rate was 5.3% (13/245) and 20.4% (20/98) for AVR and MVR, respectively. Elderly CABG patients had a hospital mortality rate of 5.8% (61/1,043) (Table 3). In-hospital mortality rates for valve

Table 3. Thirty-Day and In-Hospital Mortality Rates^a

Mortality	AVR (n = 245)	MVR (n = 98)	CABG (n = 1,043)
30-Day	3.3% (1%-5.5%)	14.3% (7.2%-21.3%)	4.7% (3.4%-6%)
In-hospital	5.3% (2.5%-8.1%)	20.4% (12.3%-28.5%)	5.8% (4.3%-7.2%)

^a Numbers in parentheses show 95% confidence interval.

AVR = aortic valve replacement; CABG = coronary artery bypass grafting; MVR = mitral valve replacement.

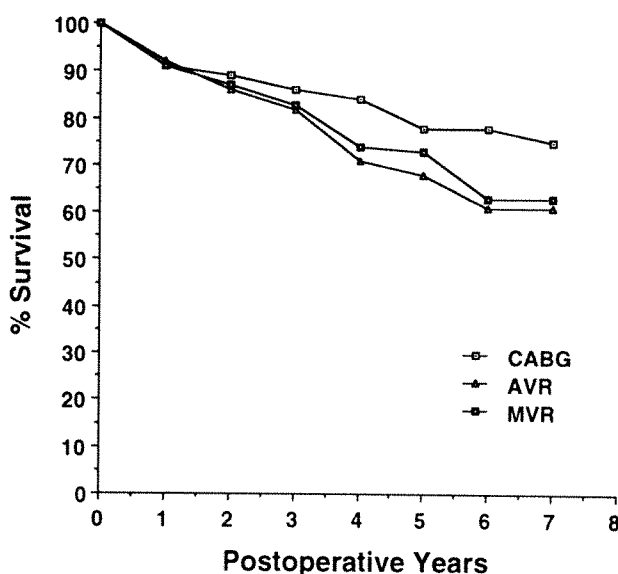


Fig 2. Actuarial survival for elderly patients undergoing aortic valve replacement (AVR), mitral valve replacement (MVR), and coronary artery bypass grafting (CABG).

replacement alone were 3.3% (4/120) for AVR and 11.4% (5/44) for MVR. Concomitant CABG increased these rates to 7.2% (9/125) for AVR and 27.8% (15/54) for MVR.

In the MVR group, 70% (14/20) of the deaths occurred in patients who were seen with ischemic valvular disease. Operation was urgently or emergently performed in 69% (9/13) of the AVR patients and 85% (17/20) of the MVR patients who died. The percentage of in-hospital deaths from cardiac-related causes was 40% (8/20) for MVR and 41% (25/61) for CABG but only 31% (4/13) for AVR. Among those patients who died in-hospital but beyond the immediate 30-day postoperative period, cardiac-related deaths were infrequent and occurred in only 2 MVR patients and no AVR or CABG patients.

Information on late mortality for patients seen in the first 2 years of the study was available on 231 (98%) of 237 patients. In particular, follow-up data were obtained on 100% (54/54) of the patients having a valve procedure. The mean duration of follow-up was 78.6 ± 7 months. Survival rates for AVR, MVR, and CABG are shown in Figure 2. Survival was similar among the three groups through 5 years of follow-up: AVR, $68\% \pm 8\%$; MVR, $73\% \pm 8\%$; and CABG, $78\% \pm 3\%$. After this, the AVR and MVR patients did significantly worse ($p < 0.05$) with 7-year survival rates of $61\% \pm 8\%$ for AVR and $63\% \pm 8\%$ for MVR compared with $75\% \pm 3\%$ for CABG.

A number of factors were analyzed as possible predictors of surgical outcome:

- Age
- Sex
- NYHA functional class
- Valvular lesion
- Stenotic
- Regurgitant

- Stenotic and regurgitant
- Left ventricular function
- Pulmonary capillary wedge pressure
- Number of critically diseased vessels
- Concomitant coronary artery bypass grafting
- Number of coronary grafts
- Type of prosthesis
 - Bioprosthetic
 - Mechanical
- Valvular pathology
 - Calcific
 - Rheumatic
 - Ischemic
 - Degenerative
 - Endocarditis

For MVR, NYHA functional class ($p = 0.03$), pulmonary capillary wedge pressure of 25 mm Hg or more ($p = 0.049$), and ischemic valvular pathology ($p = 0.01$) were significant predictors of early mortality. For AVR, only NYHA functional class was a significant correlate ($p = 0.02$). Compared with MVR patients, AVR patients were older ($p = 0.0002$), were more often male ($p = 0.006$), had a lower pulmonary capillary wedge pressure ($p = 0.0001$), and had fewer critically stenosed vessels ($p = 0.001$). By univariate analysis, neither aortic valve gradient nor aortic valve area was a significant predictor of early mortality for patients with pure aortic stenosis. Similarly, the degree of aortic or mitral regurgitation did not predict death in patients with purely regurgitant lesions. Only poor LVF was predictive of late death for MVR patients (17% versus 100% survival at 7 years; $p < 0.0005$).

Comment

Cardiac operations are being performed in elderly patients with increasing frequency and encouraging results. For example, AVR in the elderly has an operative mortality rate of 5% to 10% [1-12] with long-term survival rates similar to that of age- and sex-matched patients in the general population [8, 11]. These results have been attributed to improvements in patient selection, myocardial protection, and postoperative care.

However, the septuagenarian or octogenarian is not simply the aged equivalent of the younger patient. In the elderly patient, there is a higher incidence of coexisting and serious morbidity, which adversely affects operative outcome [10, 11, 13]. It is noteworthy that most cardiac-related deaths in this series occurred within 30 days of operation. Deaths occurring after that time but in-hospital were usually due to failure of multiple organ systems, demonstrating the precarious physiologic homeostasis present in elderly patients.

Furthermore, the elderly heart is affected by a different spectrum of diseases. With age, the aortic valve undergoes fibrosis and calcification such that senile aortic stenosis is one of the most prevalent valvular lesions in the elderly. In the present study, calcific aortic stenosis was the indication for AVR in 85% (209/245).

With advanced age also come an increased incidence of

CAD and the effect of ischemia on the myocardium and valvular function. Ischemic mitral regurgitation constitutes a sizable proportion of mitral lesions seen in the elderly. In this series, 30 MVR patients (31%) had ischemic pathology. However, this classification underestimates the true incidence of ischemic heart disease in patients undergoing MVR. As shown in Table 1, 64 (65%) of MVR patients had at least one diseased coronary artery, and 45 (46%) had severe two- or three-vessel disease. Thus, nonischemic valvular pathology did not preclude the presence of serious CAD. Nevertheless, ischemic mitral valve disease identified a subset of patients with severe CAD. The incidence of two- and three-vessel disease in these patients was 90% (27/30).

Pure calcific aortic stenosis typically causes concentric hypertrophy of the left ventricle, which may regress after relief of the outflow obstruction. In all but the end-stage case, there is usually little permanent damage to the myocardium, and patients fare well postoperatively [14]. Indeed, in our series, the early mortality rate of 5.3% for patients undergoing AVR was essentially the same as that of patients having isolated CABG (5.8%), comparable with [6, 8] or less than [3, 11] results reported in other series. Concomitant CABG increased the mortality rate from 3.3% (AVR alone) to 7.2% (AVR + CABG). This finding was also noted in other reports [1, 3, 5, 9, 10] and raises the question how aggressively revascularization should be pursued in the elderly patient with aortic valve disease, especially in the patient without demonstrable preoperative ischemia. The additional intraoperative ischemic time required for bypass grafting may not have been well tolerated. On the other hand, more advanced ventricular dysfunction in patients requiring concomitant CABG may have contributed to the increased mortality rate. Because most patients in this series with coronary lesions amenable to revascularization underwent bypass grafting, the outcome of isolated valve replacement in such patients is not known. Clearly, further studies addressing these issues are needed.

Only NYHA functional class correlated with early mortality for AVR. In particular, poor LVF did not correlate with mortality. These results are in agreement with those of Levinson and colleagues [4] in their report of AVR in octogenarians with aortic stenosis. This finding is also consistent with what is known of the natural history of aortic stenosis. Left ventricular function is well preserved until late in the course of the disease. Even then, valve replacement is sometimes curative, and ventricular function is restored to normal [14].

Long-term survival for the first 5 years after AVR paralleled that of CABG patients. The decline in relative survival thereafter is difficult to explain, as no risk factors were identified. Older age in AVR patients compared with MVR or CABG patients may have been contributory.

In contrast to calcific disease, ischemic disease may damage not only the valve but also the myocardium. In this situation, valve replacement may do little to improve left ventricular dysfunction, and the condition of patients may continue to deteriorate [15]. Seventy percent of in-hospital deaths after MVR occurred in patients with

ischemic mitral valve disease. The overall early mortality rate of 20.4% for MVR patients was substantially higher than that of the AVR or CABG group.

Multivariate analysis demonstrated that factors indicative of ischemic disease (higher pulmonary capillary wedge pressure and ischemic pathology) were the most important predictors of early death. Tsai and co-workers [9] also found that patients with acute ischemic syndromes require longer periods of cardiopulmonary bypass and cross-clamp time and have increased mortality.

Although the number of critically diseased vessels was not found to be a correlate of early death, MVR patients had substantially more CAD than AVR patients. Furthermore, MVR patients who required concomitant coronary revascularization had a substantially higher mortality rate than those who did not (27.8% versus 11.4%), possibly reflecting a greater degree of ischemic myocardial damage. This finding raises the same issues of routine revascularization in elderly patients undergoing valve replacement.

Although only 11% of MVR patients had poor LVF, this is probably an underestimation, especially given that 31% of the patients had ischemic disease and 98% were in NYHA class III or IV. Typically, LVF is determined by calculating ejection fraction from planimeter areas of left ventricular images in right anterior oblique and left anterior oblique projections. Conditions such as ischemic mitral regurgitation that decrease afterload may cause a misleading normalization of the ejection fraction despite real deterioration in function. Thus, it is likely that many more MVR patients had poorly functioning ventricles than is implied by the catheterization results.

It is interesting that poor LVF did not emerge as a significant predictor of early mortality but did correlate with poor long-term survival. It may be that valve replacement (with or without revascularization) in these patients is temporizing but not curative. Although cardiac performance is stabilized or even improved in the immediate postoperative period, LVF may continue to deteriorate further.

The published literature contains many reports on the outcome of valve operations in elderly patients. The majority of these have been written (1) to justify an aggressive surgical approach when medical therapy has failed, (2) to refute aortic valvuloplasty as a viable alternative to surgical intervention, or (3) to demonstrate acceptable mortality rates. Our study is unusual in that it examines how valvular disease in the elderly affects surgical outcome. Our results suggest that outcome after valve replacement in elderly patients is primarily a function of the damage incurred by the myocardium as a result of the primary disease, particularly the severity and extent

of CAD. Thus, most elderly patients who undergo AVR are seen with a calcified stenotic aortic valve but a well-functioning ventricle. The degree of CAD is markedly less than that in MVR patients. Operative outcome is excellent for AVR, with an early mortality similar to that of isolated CABG. In contrast, patients requiring MVR have more serious ischemic disease, which damages both valve and myocardium. Operative outcome is worse in these patients, and long-term survival is dependent primarily on LVF.

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DISCUSSION

DR CARY W. AKINS (Boston, MA): In the series you presented, were there any patients who had mitral valve reconstruction rather than mitral valve replacement? Has the team at Johns

Hopkins looked at results in that group to find out whether the results in patients who have damaged left ventricles are better if the valve can be repaired rather than replaced?

DR DAVIS: We did not include patients undergoing mitral valve repair in this study. Seventy percent of the mitral valve replacement patients who died had severe ischemic disease, typically with papillary muscle rupture or dysfunction. For such patients, valve replacement was the procedure of choice. Patients who underwent mitral valve repair had much less severe disease. Thus, a comparison of outcome for repair versus replacement would be more reflective of the patient's preoperative cardiac function than of the surgical procedure.

DR D. CRAIG MILLER (Stanford, CA): How many of the mitral valve replacements for mitral regurgitation were done with preservation of both or one of the leaflets and chordal apparatus?

DR DAVIS: I regret that I do not have the data to answer that question.

DR BRUCE A. REITZ (Baltimore, MD): Increasingly through the years the chordal apparatus was spared. However, I do not think that was specifically looked at in this study, and so I cannot answer that question.

DR MILLER: At least by inference, Dr Davis told us a minute ago that the regurgitant mitral valves really were not reparable unless you were willing to reattach ruptured papillary muscles. Could we have comments from Dr David and Dr Cosgrove about how wise (or unwise) this is in patients older than 70 years, the vast majority of whom had coronary disease?

DR TIRONE E. DAVID (Toronto, Ont, Canada): I do not repair the mitral valve in patients with ischemic mitral insufficiency, particularly when it is acute. However, when the patient has chronic insufficiency and there is also a component of myxomatous degeneration, I do undertake repair, and the results have been good. When the insufficiency is purely on the basis of papillary muscle-ventricular wall dysfunction or due to acute papillary mus-

cle rupture, I replace the mitral valve. My experience with mitral valve repair in these patients has been disappointing.

DR MILLER: You are distinguishing these patients from patients who just need a ring or a posterior ring for dilatation?

DR DAVID: In our experience, the most common cause of mitral regurgitation due to ischemia is limited mobility of the leaflets along the posteromedial commissure and not prolapse of the leaflets. In 90% of cases, the posteromedial papillary muscle and the posterior left ventricular wall do not contract well, and the wall bulges in systole. This abnormal wall motion drags the medial commissure into the ventricle. It is possible to correct the regurgitation by performing an asymmetrical annuloplasty. The fate of this type of repair is unpredictable because the left ventricle may continue to dilate and mitral regurgitation may recur.

DR DELOS M. COSGROVE III (Cleveland, OH): Ischemic mitral valve disease continues to be a very serious problem and one that has carried a high mortality. My associates and I have not been able to demonstrate that mitral valve repair has improved long-term survival. Survival after mitral valve operation for ischemic mitral disease is directly related to the function of the left ventricle. Patients with dilated left ventricles have a very poor prognosis.

DR MILLER: Doctor Davis, could you tell us how you quantified left ventricular systolic function, specifically in patients with mitral regurgitation? You mentioned that it was an adverse predictor of late survival in the patients having mitral valve replacement. You did not study just ejection fraction, I hope.

DR DAVIS: Left ventricular function was determined at catheterization by several variables: wall motion, ejection fraction, and end-diastolic pressure. Patients with poor left ventricular function typically had ejection fractions less than 0.30 and end-diastolic pressures greater than 15 mm Hg.

Damus-Kaye-Stansel With Cavopulmonary Connection for Single Ventricle and Subaortic Obstruction

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Infants with single ventricle and transposition of the great arteries with or without aortic arch obstruction have a poor prognosis due in large part to the development of systemic outflow obstruction, a frequent consequence of pulmonary artery banding. Thus, the initial palliation and long-term treatment options are critical in terms of surgical choices and timing. We report our experience with 9 patients managed by neonatal pulmonary artery banding and early debanding, a Damus-Kaye-Stansel procedure, and either a modified Glenn shunt or a modified Fontan procedure. Some evidence of subaortic stenosis developed in every patient as manifested by a resting gradient across the systemic outflow tract (21.4 ± 4.2 mm Hg), a small ventricular septal defect relative to the body surface area (1.57 ± 0.39 cm²/m²), and a small ventricular septal defect relative to the aortic root cross-

sectional area (0.70 ± 0.04 cm²/m²). There were 1 early death and 1 late death after the Damus-Kaye-Stansel procedure. With the exception of 1 patient, the in-hospital course of the survivors was relatively uncomplicated. Two patients with levotransposition of the great arteries have required pacemakers. None of the survivors have residual systemic outflow obstruction. There is trivial or mild pulmonic insufficiency in 5 patients, which is not progressing. One patient had mild to moderate pulmonic insufficiency but died late presumably of an arrhythmia. We conclude that neonatal pulmonary artery banding coupled with planned early debanding, a Damus-Kaye-Stansel procedure, and cavopulmonary anastomosis is a relatively low-risk course for patients with this complex physiology.

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The prognosis for infants with single ventricle physiology in whom subaortic stenosis either is present or develops is very poor whether or not an attempt at surgical correction is made [1-4]. This obstruction to systemic outflow occurs most frequently in the subset of infants with a dominant left ventricle, transposition of the great arteries (TGA) such that the aorta comes off the rudimentary right ventricle, and unobstructed pulmonary blood flow particularly when there is aortic arch obstruction. Systemic flow exits the heart into the aorta through a ventricular septal defect (VSD), which is usually of a muscular type (Fig 1A). To protect the pulmonary vasculature and to control heart failure, banding of the pulmonary artery (PA) has been the conventional approach along with repair of the aortic arch obstruction when present (Fig 1B). This approach frequently produces major subaortic stenosis and subsequent left ventricular hypertrophy, both adverse preoperative conditions for patients destined for a Fontan type of correction. Fewer than half the patients in whom subaortic stenosis develops after PA banding survive to even be candidates for the Fontan operation [4, 5].

Although all these patients will need a procedure to limit pulmonary blood flow, it has been suggested that PA banding be abandoned because of its tendency to produce subaortic stenosis and that initial palliation should be anastomosis of the unobstructed PA exiting the dominant ventricle to the ascending aorta, repair of the aortic arch (if necessary), and performance of a systemic-pulmonary shunt in early infancy [5-8]. This, too, carries a very high mortality rate of approximately 50% when done in infants less than 3 months of age.

Because of the bleak results of both the conventional and the more radical approaches to this group of patients, we have adopted a policy of PA banding with arch repair in the newborn period followed by early takedown of the PA band coupled with a Damus-Kaye-Stansel (DKS) procedure (proximal PA-ascending aorta anastomosis) and cavopulmonary anastomosis (modified Glenn shunt or Fontan procedure). This report summarizes our results with this approach.

Material and Methods

Patient Population

We reviewed the records of all patients who underwent a DKS procedure with cavopulmonary connection at St. Louis Children's Hospital. There were 9 such patients, 5

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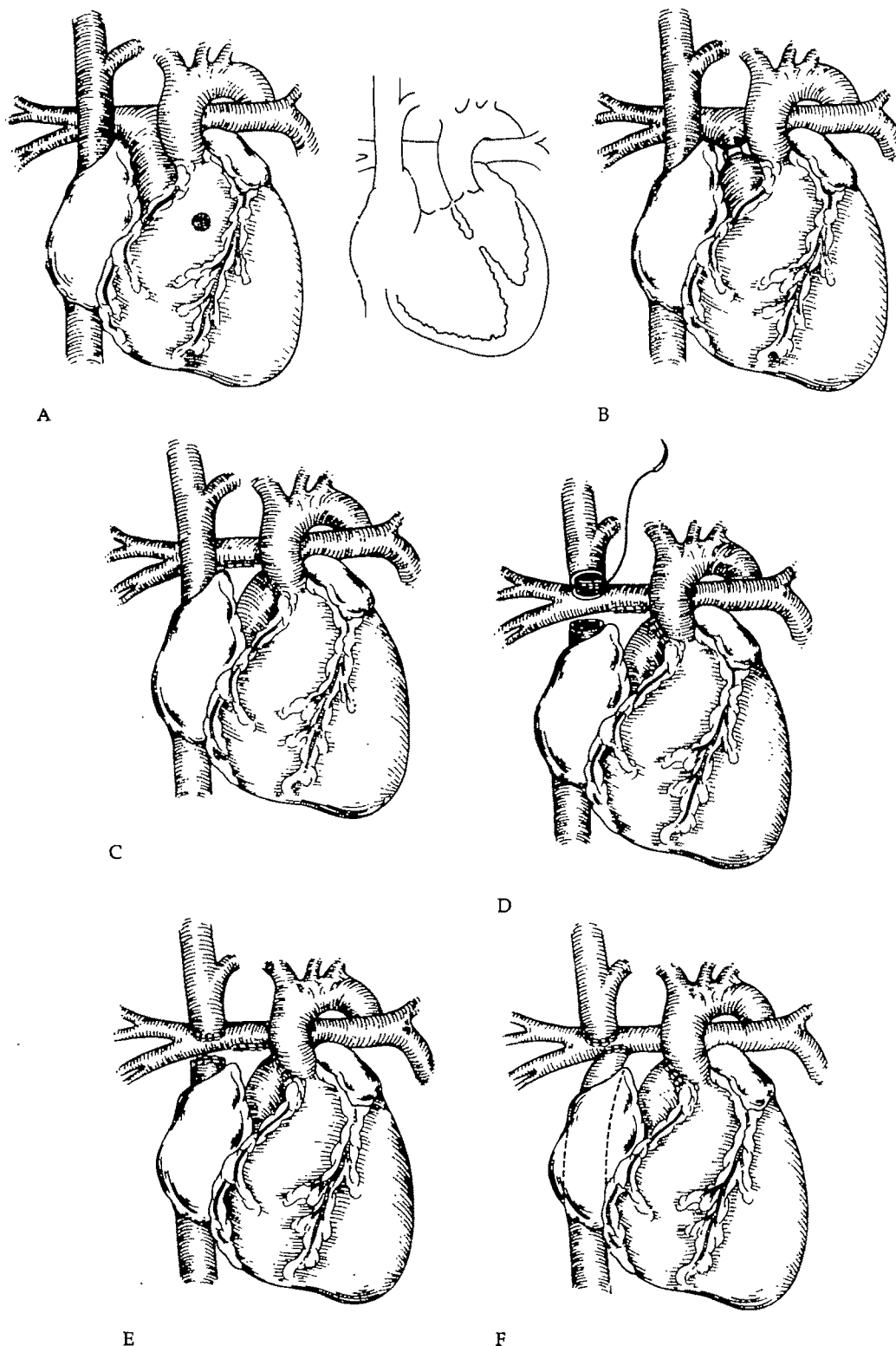


Fig 1. (A) The typical anatomy for these patients is the aorta coming off a rudimentary right ventricle and the pulmonary artery, off the left ventricle. Systemic outflow reaches the aorta through a muscular ventricular defect (speckled area in the drawing on the left). (B) Pulmonary artery banding is the initial palliative procedure. (C) The Damus-Kaye-Stansel procedure is performed by dividing the pulmonary artery at the band site, anastomosing it end-to-side to the ascending aorta, and oversewing the distal main pulmonary artery. (D) The superior vena cava is then divided and its distal end sewn end-to-side to the right pulmonary artery, thus creating the modified Glenn shunt. (E) The proximal superior vena cava is oversewn if the patient is not a candidate for the modified Fontan correction. (F) For a candidate for the Fontan procedure, an atrial baffle is created to divert the inferior vena cava blood to the superior vena cava, which is then anastomosed end-to-side to the inferior aspect of the right pulmonary artery or to the distal end of the transected main pulmonary artery.

Table 1. Summary of Patient Data

Patient No.	Anatomic Diagnosis	Initial Palliation	Age at PAB (d)	Age at DKS Procedure (mo)	Outcome
1	TA, D-TGA, CoA	PAB, repair of CoA	21	10 ^a	Alive and well
2	SV, CAVC, D-TGA	PAB	14	5 ^a	Alive; Fontan at 35 mo
3	DILV, L-TGA	PAB	48	16 ^a	Alive; developed heart block requiring pacemaker
4	TA, D-TGA, IAA	PAB, repair of IAA	6	12 ^a	Alive; Fontan at 35 mo
5	TA, L-TGA, CoA	PAB, repair of CoA	93	11 ^a	Died late of arrhythmia
6	MV atresia, hypoplastic LV, CoA	PAB, repair of CoA	17	14 ^b	Died postop of CNS event
7	TA, D-TGA	PAB	44	34 ^b	Alive and well
8	TA, L-TGA, situs inversus	PAB	48	37 ^b	Alive; required closure of aortopulmonary fistula
9	DILV, D-TGA, CoA	PAB, repair of CoA	2	15 ^b	Alive; intermittent heart block requiring pacemaker
Mean	...	...	32 ± 5	17 ± 3	...

^a Damus-Kaye-Stansel procedure was performed in combination with a modified Glenn shunt.

^b Damus-Kaye-Stansel procedure was performed in combination with Fontan procedure.

CAVC = complete atrioventricular canal; CNS = central nervous system; CoA = coarctation of aorta; DILV = double-inlet left ventricle; DKS = Damus-Kaye-Stansel; D-TGA = dextrotransposition of the great arteries; IAA = interrupted aortic arch; L-TGA = levotransposition of the great arteries; LV = left ventricle; MV = mitral valve; PAB = pulmonary artery banding; SV = single ventricle; TA = tricuspid atresia.

of whom underwent a modified Glenn shunt at the time of the DKS procedure and 4, a modified Fontan procedure. Their characteristics are summarized in Table 1.

All patients were treated initially with PA banding, and 5 also required repair of aortic arch obstruction (coarctation of the aorta or interrupted aortic arch). The primary cardiac diagnoses in all patients were some variation of single ventricle with TGA and unobstructed pulmonary blood flow. Five patients had tricuspid atresia, 2 had double-inlet left ventricle, and two others had complex single-ventricle variants. The average age at PA banding was just older than 1 month, and the average age at the DKS procedure was 17 months. Those undergoing a DKS operation with a modified Glenn shunt were operated on at an earlier age (average age, 10.8 ± 1.9 months; range, 5 to 16 months) than those undergoing this operation with a modified Fontan procedure (average age, 25.0 ± 3.5 months; range, 14 to 37 months). Their medical records, echocardiograms, and cardiac catheterization results were examined. Follow-up was 100%.

The echocardiograms were reviewed by a single individual (C.E.C.) to assess the size of the VSD, the degree of ventricular hypertrophy, the ventricular chamber dimensions, and the presence of postoperative pulmonic insufficiency (PI). Pulmonic insufficiency was graded according to the size of the regurgitant jet: trivial = barely perceptible with color flow Doppler, mild = a very small jet beneath the semilunar valve, and mild to moderate = slightly greater than barely beneath the valve. The VSD size was measured in a fashion similar to that described by Matitiau and co-workers [9]. Relative size of the VSD was then appraised by relating it to the body surface area of the patient and to the aortic root cross-sectional area. Ventricular hypertrophy was assessed by measuring the

thickness of the posterior and septal walls of the dominant ventricle in diastole. The end-diastolic diameter of the dominant ventricle was measured at the level of the papillary muscles. The ventricular wall thickness and end-diastolic diameter were related to echocardiographically obtained normal values in growing children [10].

Follow-up information was derived from outpatient visits at St. Louis Children's Hospital or by communication with the local physician.

Surgical Procedure

Through a median sternotomy, the patients were placed on standard cardiopulmonary bypass using bicaval cannulation. The superior vena cava was cannulated at its junction with the innominate vein. Systemic cooling was performed to 28°C, and the heart was arrested with hyperkalemic cold crystalloid cardioplegia. The main PA was divided just proximal to the band, and the distal end was oversewn (Fig 1C). An appropriate site on the ascending aorta was selected for the main PA-aorta anastomosis, this usually being on the posterior surface just above the commissures of the aortic valve. A small segment of aorta was excised, and the anastomosis was constructed using monofilament absorbable suture. For those patients undergoing a bidirectional Glenn shunt, the aortic cross-clamp was removed at this point (Figs 1D, 1E). The superior vena cava was divided just above the right atrium, and its proximal end was oversewn. The distal end was then sewn end-to-side to the right PA. For patients undergoing the modified Fontan procedure, closure of the atrial septal defect and atriopulmonary anastomosis were carried out with the cross-clamp applied (Fig 1F).

Table 2. Assessment of Subaortic Obstruction^a

Variable	Initial	Before DKS Procedure
Pressure gradient (mm Hg)	... ^b	21.4 ± 4.2
VSD size (cm ²)	0.61 ± 0.25	0.68 ± 0.27
VSD/BSA ratio (cm ² /m ²)	2.63 ± 0.79	1.57 ± 0.39
VSD/aortic root area ratio	1.03 ± 0.05	0.70 ± 0.04

^a Data are shown as the mean ± the standard error of the mean. ^b Not all patients underwent cardiac catheterization when first seen; data are incomplete.

BSA = body surface area; DKS = Damus-Kaye-Stansel; VSD = ventricular septal defect.

Results

Data are expressed as the mean ± the standard error of the mean.

Degree of Subaortic Stenosis

The degree of subaortic stenosis was evaluated using the resting gradient across the VSD at cardiac catheterization and by assessing the size of the VSD on echocardiography in relation to the body surface area and the cross-sectional area of the aortic root (Table 2). The mean gradient was 21.4 mm Hg (range, 5 to 55 mm Hg). The VSD size at initial evaluation was 0.61 ± 0.25 cm² and increased minimally to 0.68 ± 0.27 cm². This was related to the growth and size of the patient in two ways. The mean VSD to body surface area ratio at initial evaluation (approximately 1 month of age) was 2.63 ± 0.79 cm²/m². This corresponds to the value suggested by Matitau and colleagues [9] to be not predictive of the development of major subaortic stenosis in this setting. However, at follow-up evaluation this value dropped to 1.57 ± 0.39 cm²/m², which is predictive of critical subaortic stenosis. The corresponding values for the ratio of the VSD to aortic root cross-sectional area were 1.03 ± 0.05 initially and 0.70 ± 0.04 at follow-up. Thus, the size of the VSD decreased on a relative basis after PA banding and became significantly obstructive.

Ventricular Dimensions

Measurements of the ventricular dimensions were also performed echocardiographically to assess chamber size and degree of ventricular hypertrophy (Fig 2). These were expressed as percent of normal. The initial echocardiogram was obtained when the patient was about 1 month of age; the next, during the same hospitalization as the DKS procedure; and the follow-up echocardiogram, at a mean of about 4 months after the DKS procedure. The degree of ventricular hypertrophy increased during the time that the PA band was in place and remained essentially unchanged at early follow-up. The end-diastolic diameter increased somewhat as well, but then returned to slightly less than the initial value in the follow-up study.

Hemodynamics Before DKS Procedure

The preoperative assessment of the integrity of the pulmonary vasculature revealed an average mean PA pres-

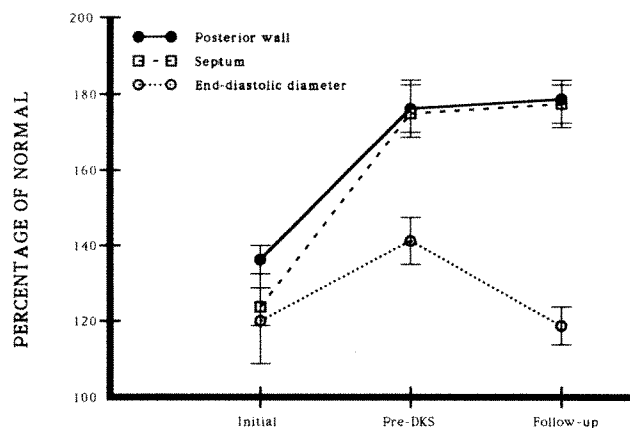


Fig 2. Changes in ventricular posterior and septal wall thicknesses and ventricular end-diastolic diameter over time as assessed by echocardiography. After pulmonary artery banding (Initial), there is obvious development of ventricular hypertrophy, which persists at early follow-up (mean time, about 4 months). The ventricular end-diastolic diameter, an estimation of ventricular volume, increases until the Damus-Kaye-Stansel (DKS) procedure is performed and then falls back to nearly normal levels.

sure of 19.6 mm Hg and an average pulmonary vascular resistance of 1.9 Wood units with a pulmonary to systemic flow ratio of 1.7:1 and a left ventricular end-diastolic pressure of 7.3 mm Hg (Table 3).

Operative Results

The operative procedures were performed using standard cardiopulmonary bypass in all patients except 1 who required circulatory arrest. The average bypass time was 88.3 minutes, and the average aortic cross-clamp time was 38 minutes (Table 4).

Eight of the 9 patients had excellent hemodynamics when they were taken from the operating room; 1 patient required a high central venous pressure of 20 to 22 mm Hg. This patient had atresia of the left atrioventricular valve and a hypoplastic left ventricle with a dominant right ventricle. His preoperative evaluation revealed relatively high pulmonary vascular resistance.

Table 3. Cardiac Catheterization Data Before Damus-Kaye-Stansel Procedure^a

Variable	Value
Right atrial pressure (mm Hg)	7.6 ± 1.7
Mean PA pressure (mm Hg)	19.6 ± 3.3
Pulmonary vascular resistance (Wood units)	1.9 ± 1.2
Q _p /Q _s	1.7 ± 0.9
LVEDP (mm Hg)	7.3 ± 2.0
SaO ₂ (%)	79.6 ± 2.6

^a Data are shown as the mean ± the standard error of the mean.

LVEDP = left ventricular end-diastolic pressure; PA = pulmonary artery; Q_p = flow to pulmonary vascular bed; Q_s = flow to systemic vascular bed; SaO₂ = systemic arterial oxygen saturation.

Initially he had a modified Blalock-Taussig shunt in conjunction with the DKS procedure but could not be weaned from cardiopulmonary bypass because of poor oxygenation. The shunt was taken down, and his correction was converted to a modified Fontan procedure. The patient then was successfully weaned from cardiopulmonary bypass albeit with somewhat unstable hemodynamics. His condition was improving, but evidence of brain death suddenly developed about 12 hours postoperatively. Postmortem examination showed brain edema only as the cause of death.

There were only 2 patients with early complications. One had mild pleural effusions. In the other, severe chylothorax and respiratory failure complicated by *Candida* sepsis developed. This was caused by a persistent aortopulmonary fistula between the proximal and distal PA after a DKS procedure with a Fontan procedure. Once this fistula was divided, the patient had a completely unremarkable postoperative course.

Follow-up

The average follow-up is 22.2 months for the survivors (Table 5). There was 1 late death. This occurred in a patient with tricuspid atresia, TGA, and coarctation who underwent a DKS procedure with a modified Glenn shunt at 11 months of age. He had a completely unremarkable postoperative course and was discharged after 5 days. He died suddenly at home of a presumed arrhythmia; at postmortem examination, he had a markedly hypertrophied ventricle but no other major findings.

To date, late complications have occurred in 2 patients. Both required a permanent pacemaker for bradyarrhythmias: complete heart block in 1 and second-degree heart block in the other. Both patients have levo-TGA and single ventricle. All the survivors are in class I. Two of the 5 patients treated with a modified Glenn shunt have since undergone completion of the modified Fontan procedure.

Assessment of the DKS anastomosis during follow-up has been done by echocardiography in all 8 operative survivors. At 1 week postoperatively, 6 of the 8 had some degree of PI: trivial or mild in 5 and mild to moderate in 1. At an average of 16 months later, none of these patients has shown progression of PI, and in 2, it has been downgraded from mild to trivial. The 1 patient with mild to moderate PI is the patient who died suddenly presum-

Table 5. Summary of Follow-up Data

Variable	Value
Mean follow-up (mo)	22.2 $\pm$ 3.1
Late deaths	1
Complications	
Pacemaker insertion	2
Gradient across DKS	0 (by echo)
Presence of PI by echo (early/late)	
Trivial	1/3
Mild	4/2
Mild to moderate	1/0 ^a

^a The patient with mild to moderate PI early postoperatively died late.

DKS = Damus-Kaye-Stansel; PI = pulmonary insufficiency.

ably of an arrhythmia. None of the patients have any evidence of a gradient across the new outflow tract of the single ventricle.

Comment

Although originally proposed as treatment of TGA [11-14], the DKS procedure has provided greater versatility for the treatment of other, more complex congenital cardiac anomalies [13]. It seems particularly well suited for circumstances in which an otherwise normal pulmonary valve and proximal main PA exit a single ventricle with an aorta and aortic valve exiting a rudimentary ventricle within which there is partial obstruction in the form of a restrictive VSD. If the Fontan procedure is to be performed, this pulmonary valve is a dead end for outflow from the single ventricle if not used in the systemic circulation to relieve the obstruction there.

There are sufficient data at present demonstrating the risk of development of subaortic stenosis in infants with single ventricle, unobstructed pulmonary blood flow, and transposed great arteries after PA banding, particularly in the presence of aortic arch obstruction [5, 15]. Whether this is linked to PA banding or is an inevitable consequence of the embryologic matrix from which this set of cardiac anomalies arises is unknown. Because the subaortic stenosis is generally in the form of a restrictive VSD, which is usually of a muscular variety, ascribing this to the generalized hypertrophy that PA banding produces has been a popular explanation for other investigators [5, 6]. Outflow obstruction ordinarily will occur within the first 3 years of life in the vast majority of these children. It provides the substrate for the subsequent development of severe hypertrophy of the dominant ventricle, the implications of which are important for an ultimate Fontan or ventricular septation procedure in terms of candidacy for the operation or operative risk [1-3, 16].

The explanation for this increased risk is perhaps related to changes in the compliance characteristics of the hypertrophied ventricle, susceptibility of the hypertrophied ventricle to ischemia at the time of operation, and "masked" elevation of the pulmonary vascular resistance

Table 4. Operative Data and Early Outcome^a

Variable	Value
Pump time (min)	88.3 $\pm$ 5.5
Aortic clamp time (min)	38.0 $\pm$ 3.6
Operative deaths	1/9
Complications	2/9
Pleural effusions	2
Sepsis	1 ^b
Aortopulmonary fistula	1 ^b

^a Where applicable, data are shown as the mean $\pm$ the standard error of the mean. ^b This was the same patient.

that occurs in spite of adequate PA banding. The hypertrophied ventricle is at risk for ischemic changes and subsequent fibrosis on the basis of differences in coronary blood flow dynamics (diminished cross-sectional area of coronary vascular bed relative to volume of myocardium [17]) as well as differences in metabolic capacity (diminished ratio of mitochondrial mass per cell mass [18] or diminished mitochondrial function [19]). Further, recovery from global ischemia of the hypertrophied ventricle is worse than for a normal ventricle and predisposes to systolic and diastolic dysfunction postoperatively [20], resulting in elevated systemic and pulmonary vascular resistances after Fontan procedures. Thus, the prevention or relief of subaortic stenosis is a critical issue in these patients.

The definition of subaortic stenosis or narrowing of the VSD in this setting is important, as is its early recognition. By the time a large systolic gradient exists between the dominant ventricle and the ascending aorta, development of severe ventricular hypertrophy will have occurred. One way to identify this early is to define the presence of subaortic stenosis as a low resting gradient (>10 mm Hg) [3, 5]. This may become more evident when measured under the provocation of a β -agonist such as isoproterenol hydrochloride, a particularly sensitive method, as the VSD is nearly always muscular in type. Other methods relate the actual size of the VSD to either body size [9] or diameter of the aortic annulus or ascending aorta [3, 5]. It is possible to measure accurately the dimensions of a VSD with the refinement of current two-dimensional echocardiography. In the newborn, it is frequently difficult to accurately assess the gradient across the VSD because of low cardiac output and congestive heart failure. Therefore, measuring the size of the VSD and relating it to body surface area or aortic root area may provide a useful index to predict the subsequent development of subaortic stenosis and also provides a noninvasive means of assessment [9].

To relieve subaortic stenosis, other methods have been proposed, including the arterial switch procedure, enlargement of the VSD, and placement of an apical ventricular-aortic conduit [2, 3]. There is limited experience in performing the arterial switch procedure for patients with this set of anomalies. The arterial switch is actually a complex modification of the simpler DKS approach. Enlargement of the VSD has been the strategy employed previously by a number of groups. It has the advantage of a direct attack on the problem and has been successful. However, there are risks of injury to the conduction system because of the variability of its position in these patients with complex physiology [21], and recurrence of obstruction can occur, particularly when a straddling valve apparatus impinges on this opening and thus limits the amount of muscle that can be safely resected. Conduits from the apex of the dominant ventricle to the descending thoracic aorta have been used but have the obvious disadvantage of requiring replacement at intervals, long-term anticoagulation, or both.

Although early experience with the DKS procedure in complex TGA or single ventricle with TGA was marked by

relatively high mortality, particularly when performed in infants [3, 5, 14], recent results in an older patient population have been excellent [22, 23]. Our results corroborate those reported by others using the DKS procedure in combination with a cavopulmonary anastomosis in terms of early mortality and overall hemodynamic status postoperatively. For these infants to reach an age at which it is appropriate to perform a cavopulmonary anastomosis, however, control of pulmonary blood flow in early infancy is mandatory and was accomplished in our series with PA banding. We recognize the long-term risk and potential sequelae of this procedure in infants with single ventricle and transposed great vessels and therefore recommend early debanding and conversion to the DKS and Glenn procedures before critical subaortic stenosis and ventricular hypertrophy occur. This is reflected in the relatively early age at operation in our patient population, particularly for those who underwent the modified Glenn shunt, but also for those who had a Fontan repair at the time of the DKS procedure.

Admittedly, rather than being constructed in a prospective fashion, our therapeutic policy has evolved over the past 4 years, with a trend toward earlier performance of a DKS procedure with cavopulmonary anastomosis. Initially, the decision to intervene with the DKS procedure was delayed until there was a major gradient across the VSD, resulting in 2 patients being followed up for nearly 3 years before that procedure. More recently, however, we have adopted the policy of a planned DKS procedure at 6 to 12 months in conjunction with a modified Glenn shunt. In spite of this, a degree of ventricular hypertrophy occurred and was still present at early follow-up. It is anticipated that some of the hypertrophy will regress as the child grows.

A legitimate concern in patients undergoing the DKS procedure involves the long-term fate of the semilunar valves. Chin and associates [24] demonstrated PI of a mild degree in 24% of patients overall after PA-ascending aorta anastomosis, primarily for hypoplastic left heart syndrome. In our early follow-up, the majority of patients had some demonstrable PI, although it was trivial or mild in nearly all of them. The later follow-up echocardiograms have not demonstrated any progression of PI whatever. The ventricular end-diastolic diameter had decreased in all of these patients compared with the measurements obtained before the DKS procedure, and none of these patients are symptomatic. This may be the consequence of distortion of the proximal PA and valve where it is attached to the ascending aorta. It is important not to stretch the proximal PA at the time of the DKS operation and to use prosthetic material if necessary to augment the length of the PA [22, 23].

For those patients in whom complete correction (ie, Fontan procedure) was not planned, a bidirectional cavopulmonary, or modified Glenn, shunt was performed. This shunt has advantages over a systemic-pulmonary shunt [25, 26] in that it does not produce a volume-overloaded ventricle, is less likely to produce PA distortion, and will not produce late pulmonary hypertension. One disadvantage is the occasional occurrence of inade-

quate pulmonary blood flow resulting from unrecognized venous collaterals connecting the superior vena cava to the azygos or hemiazygos veins, thus allowing drainage of superior vena caval blood into the inferior vena cava with bypass of the lungs. There is also some risk of the development of pulmonary arteriovenous fistulas, which has been associated with extended age of the shunt. Most of these children, however, will have a Fontan repair within 2 to 3 years, and although these fistulas are reported to occur in patients after the Fontan procedure [27], this is unusual.

Is PA banding for single ventricle with TGA a procedure ready to go the way of the dinosaur [6]? It remains a relatively safe and effective means of palliation for these infants with heart failure caused by unobstructed pulmonary blood flow, particularly in the absence of subaortic stenosis at presentation. However, outflow to the aorta through the VSD will decrease and the dominant ventricle will predictably hypertrophy in this setting, as is clearly seen in our study. For this reason, the PA band must be taken down early for further palliation before oxygen saturation worsens. In fact, many of these children will maintain adequate oxygenation, as the subaortic stenosis tends to maintain the rightward balance of the right-to-left shunt by its leftward restriction. Some authors [5, 6, 8, 23] recommend performance of the DKS procedure with a systemic-pulmonary shunt during the neonatal period to avoid the disadvantages of PA banding. As noted already, however, systemic-pulmonary shunts carry risks of their own; further, this produces a volume-overloaded single ventricle. We believe that the combination of neonatal PA banding and a DKS procedure plus a Glenn shunt at age 6 to 12 months overall carries a lower risk than a neonatal DKS procedure with systemic-pulmonary shunting and should produce a good candidate for the Fontan procedure at 18 to 36 months of age.

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DISCUSSION

MR BABULAH SETHIA (Birmingham, England): I congratulate you on your results. Over the last 3 years, my colleagues and I have had a similar experience. We have performed a Damus-Kaye-Stansel procedure in association with cavopulmonary connection on 6 patients. There was one death. During this time, we also have had 1 infant who died at the age of 8 months while waiting for a cavopulmonary connection. Do you think that waiting up to 2 years for a Fontan procedure is perhaps a little long for patients with this particular pathology? Would you consider performing this sort of bidirectional cavopulmonary anastomosis relatively early, particularly in view of the experience with management of hypoplastic left heart syndrome, perhaps about the age of 6 months, to reduce this risk of sudden, unexpected early death?

DR HUDDLESTON: I appreciate your comments and questions. The older infants in this study were operated on relatively early in our experience. Our policy now is to perform the modified Glenn shunt, or bidirectional cavopulmonary connection, with the Damus-Kaye-Stansel procedure at the age of 6 to 12 months, and we are leaning more toward the 6-month period. Thus, we agree that the earlier the procedure is performed, the safer it probably is.

DR HILLEL LAKS (Los Angeles, CA): I compliment you on an excellent presentation. There had been fear that if the pulmonary artery in infants or neonates is banded in the presence of subaortic stenosis, they would not be able to tolerate it. In fact, we have not seen this. Even in patients who have slight gradients and do not require an immediate Damus-Kaye-Stansel procedure and in neonates with 15 or 20 mm Hg gradients, application of the band has not aggravated the situation, and they have tolerated it well.

Our approach is similar to yours: very early placement of a band, preferably in the first few weeks of life, and then an elective Damus-Kaye-Stansel procedure combined with a bidirectional Glenn shunt. If there is any gradient at all, we like to do this early, as early as 4 months, to avoid the hypertrophy that has been associated with mortality for the subsequent Fontan procedure.

I have a few comments on the technique of doing the Damus-Kaye-Stansel procedure. We think that to try to bring the pulmonary artery directly up to the aorta will result in pulmonary regurgitation, as you experienced, and we believe it should never be brought up without a patch. We have divided our 29 patients with a Damus-Kaye-Stansel procedure into those whose band is very proximal and those whose band is very distal. In those with a very proximal band, we make a transverse incision in the aorta immediately adjacent to the top of the pulmonary artery and then create a triangular flap in the aorta above that transverse incision. Pericardium is bridged over to roof the two arteries. Only in patients with a very distal band do we make a vertical extension of that incision into the main pulmonary artery, stopping above the commissures in order not to distort the valve. I think one of

the major defects of this procedure is the potential for pulmonary regurgitation, and techniques have to be adopted very carefully to avoid that complication.

DR HUDDLESTON: That is a very good comment. I agree that stretching the pulmonary artery is going to cause problems and that prosthetic materials should be used whenever necessary. At the time of the banding procedure, I think it is good to go ahead and put the band in a relatively distal position on the main pulmonary artery, given the fact that it is very short in a 1-month old baby, and thus allow for a bit more length in the proximal main pulmonary artery to use for the Damus-Kaye-Stansel connection.

DR MARSHALL L. JACOBS (Philadelphia, PA): I congratulate Dr Huddleston and his associates for their excellent results in managing this difficult problem. I have one comment and one question. I think Drs Damus, Kaye, and Stansel would be flattered to know that the principle of associating the proximal main pulmonary artery with the aorta has found wide application. However, technically speaking, I believe that the Damus-Kaye-Stansel operation is an operation for transposition of the great arteries that also includes the interposition of a conduit between the right ventricle and the pulmonary arteries.

My question is the following: In neonates, as you said, it is very difficult, often impossible, to accurately measure the degree of obstruction between the systemic ventricle and the aorta, particularly when there is a widely patent ductus arteriosus. I suggest that in those infants with aortic arch obstruction, its presence is indicative of already existent obstruction of flow into the aorta, and that hypoplasia or underdevelopment of the arch is reflective of the presence of that lesion. In that instance (if you were convinced of the presence of subaortic obstruction), would you not associate the main pulmonary artery with the aorta in the infant as part of the initial procedure? If that were done, might you not reduce the incidence of pulmonary insufficiency that may be associated with pulmonary artery banding?

DR HUDDLESTON: Such a Norwood type of operation, if you would refer to it as that, subjects the patients to a relatively high operative risk, at least in our experience. The degree of obstruction, as assessed probably most accurately with echocardiograms, would weigh in our decision about which procedure to perform as the initial one. We have performed this pulmonary artery-aorta anastomosis as the initial procedure in some neonates with very similar physiology and what was considered to be severe outflow tract obstruction. Pulmonary artery banding in this situation would be a relatively high-risk procedure because it would produce obstruction to both outlets of a single ventricle. However, for less severe obstruction, we believe the relative safety of pulmonary artery banding and the risk of later mild pulmonary insufficiency outweigh the high risk of a neonatal Damus-Kaye-Stansel procedure.

Atrioventricular Canal Defect: Two-Patch Repair and Tricuspidization of the Mitral Valve

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Between November 1978 and May 1991, a two-patch repair with tricuspidization of the left atrioventricular valve was performed in 104 patients with complete atrioventricular canal defect. Mean age was 12 months for the 68 patients who underwent primary repair and 22 months for the 36 patients who had previous pulmonary artery banding. Eleven patients died within 30 days of operation and 4 died late. Reoperation was carried out in 2 patients. Eighty-six patients were in sinus rhythm after operation. One patient required a permanent pacemaker

for complete heart block. Follow-up data for 1 to 13 years are available in 80 of 89 survivors (90%). Actuarial survival at 13 years is 81% and event-free survival is 92%. Seventy-six patients are in New York Heart Association class I and 4 in class II. Postoperative echocardiogram of these patients showed minimal or no mitral regurgitation. The advantages of this technique are preservation of valve integrity, durable mitral valve repair, and rare reoperation or heart block even in younger patients.

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Mitral regurgitation and reoperation remain the two most important complications in patients undergoing repair of complete atrioventricular (AV) canal defect [1-4]. Successful surgical repair must include competence and durability of the mitral valve and elimination of reoperation [5]. We report here our experience with the repair of complete AV canal carried out using a two-patch technique in 104 consecutive patients between November 1978 and May 1991. The results, the durability of the repair, freedom from patch dehiscence, reoperation, complete heart block, and left ventricular outflow tract obstruction are analyzed.

Material and Methods

Between November 1978 and May 1991, 104 patients underwent repair of AV canal defect using a two-patch technique at Children's Hospital of Buffalo and more recently at Miami Children's Hospital. Thirty-six patients had undergone previous pulmonary artery banding with ligation of a patent ductus arteriosus, and 68 patients underwent primary repair. At the time of definitive repair, age ranged widely from 5 months to 5.5 years. Twenty-one patients were less than 1 year old, 42 between 1 and 2 years, and 41 older than 2 years.

Mean age was 12 months at primary repair and 22 months in banded patients. Associated cardiac anomalies were present in 40 patients. These were patent ductus arteriosus in 24 patients, atrial septal defects in 10, valvar pulmonic stenosis in 2, double mitral valve orifice in 2, bicuspid aortic valve in 1, and left superior vena cava in 1 patient. All patients had preoperative cardiac catheterization, angiocardiology, and echocardiography.

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The mitral valve was fully competent in 26 patients, mildly regurgitant in 50, moderately regurgitant in 21, and severely regurgitant in 7 patients as evaluated by preoperative angiocardiology. The repair was done using a two-patch technique described by us [6]. The operations were performed on conventional cardiopulmonary bypass and cold potassium cardioplegia. In infants, deep hypothermia with circulatory arrest was used. The ventricular component was closed using a Dacron patch and the atrial component was closed with a pericardial patch. The common AV valve was sandwiched between these patches without closing the "cleft," which resulted in a trifoliate left AV valve. The configuration of the right AV valve component was not considered to be critical. The competence of the left AV valve was tested by injecting saline solution into the left ventricular cavity. If the competence of the valve appeared to be compromised by the cleft, the cleft was progressively closed, completely if necessary. In 11 patients who had residual mitral regurgitation, closure of the cleft resulted in restoration of competence. In 93 patients, valves were tricuspidized and found to be fully competent.

Results

Early Deaths

Eleven patients died within 30 days of operation while in the hospital. Three patients died of grade IV pulmonary vascular obstructive disease, 3 of severe mitral regurgitation, 2 of intractable arrhythmia, 1 of postoperative hemorrhage, 1 of low cardiac output syndrome, and 1 of aspiration pneumonia.

Late Deaths

Four patients died in the follow-up period: congestive heart failure developed in 2, 1 died of hemorrhage at

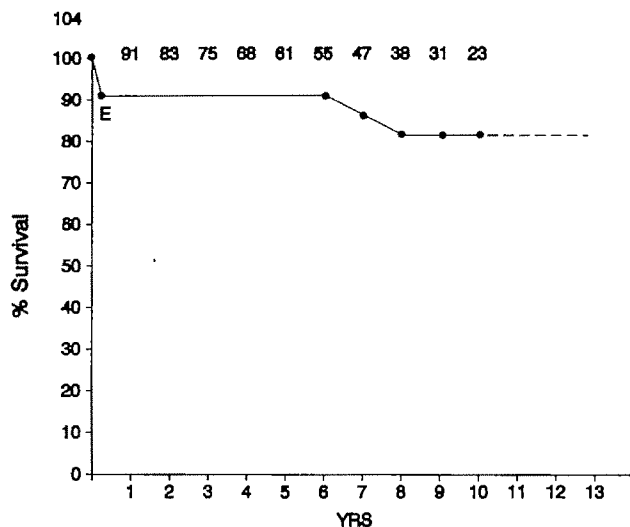


Fig 1. Actuarial survival (numbers of patients at risk are above the survival line). (E = early death.) (Reference: Berkson J, Gage RP, Mayo Clin Proc 1959).

reoperation for replacement of mitral valve, and in 1, patch dehiscence was found at autopsy.

Postoperative Rhythm

In the early postoperative period, 86 patients were in normal sinus rhythm and 17 in junctional rhythm with good hemodynamics. Complete heart block developed in 1 patient and necessitated placement of a permanent pacemaker.

Reoperation

Two patients required reoperation. One died of hemorrhage in the postoperative period after replacement of the mitral valve, and the other patient had mitral valve repair with good result.

Follow-up data for 1 to 13 years are available in 80 of 89 survivors. Patients who were lost to follow-up were mostly from outside the country. Seventy-six patients are in New York Heart Association class I and 4 in class II. The actuarial probability of survival at 13 years is 81% (Fig 1).

Comment

Repair and Mitral Competence

Rastelli-type repair has the potential drawbacks of mitral regurgitation and patch dehiscence [7-9]. The Rastelli repair requires division of the common anterior and posterior leaflets and a single patch to close the atrial and ventricular components. The divided leaflets are resuspended and the cleft of the anterior leaflet of the mitral valve is closed [12]. Division of leaflet and resuspension results in loss of valve tissue; closure of the cleft results in restricted mobility of the newly created anterior leaflet. The single Dacron patch creates the potential for hemolysis in the presence of residual regurgitation.

Carpentier's [11] studies showed that after the repair of

AV canal the mitral valve should be trifoliate. However, creation of trileaflet mitral valve as described by Carpentier requires extensive leaflet mobilization and chordal resection. This may not be necessary because most of these valves are competent preoperatively. These concerns led us to develop the two-patch repair of AV canal with tricuspidization of the left AV valve at Buffalo Children's Hospital in November 1978. We continued using this procedure in all patients at Buffalo Children's Hospital and more recently at Miami Children's Hospital. A two-patch repair with complete closure of the cleft was reported by Trusler [12]. In our technique, no portion of the valve leaflet or any chordal attachment is divided to preserve the integrity of the bridging leaflets. While the Dacron patch is attached to the ventricular crest, sutures are passed between the chordae of the AV valve. This maneuver avoids the necessity of dividing any chord. The left AV valve is sandwiched between the two separate patches used to close the ventricular and the atrial components of the defect. The mitral "cleft" is not sutured, because the tricuspidized mitral valve is fully competent and complete closure of the "cleft" may reduce the orifice area, rendering the valve stenotic and partially immobilizing the new anterior leaflet. This important fact has been emphasized recently by other authors [13, 14]. Recent anatomic observations have further clarified the surgical anatomy and emphasized the trileaflet configuration of mitral valve in AV canal defects [15, 16].

Associated Secundum Atrial Defect

Early in our experience, the tissue between the secundum atrial septal defect and primum defect was divided, which resulted in distortion of the AV valve geometry and necessitated reconstitution of this bridge. At present, if the exposure is adequate, this bridge of tissue is not divided and both defects are covered with a single pericardial patch.

Reoperation

Reoperations have been reported for mitral valve incompetence, patch dehiscence, and residual ventricular septal defect. In this series, using the two-patch technique we have achieved a fully competent mitral valve in all surviving patients with only two reoperations for mitral regurgitation. Because the AV valve is competent in most patients preoperatively, preservation of the valve geometry at the time of repair should assure full postoperative competence.

This can be achieved by accurately assessing the height of the valve, anchoring the valve to the septal patch without any distortion, and maintaining mitral and tricuspid continuity. Sandwiching the AV valve between the ventricular and atrial patches provides a buttressing effect to the valve, which prevents sutures cutting through the valve leaflets, minimizing the chance of dehiscence. This load-distribution reinforcement suture technique was experimentally shown by Katz and colleagues [17] to eliminate dehiscence.

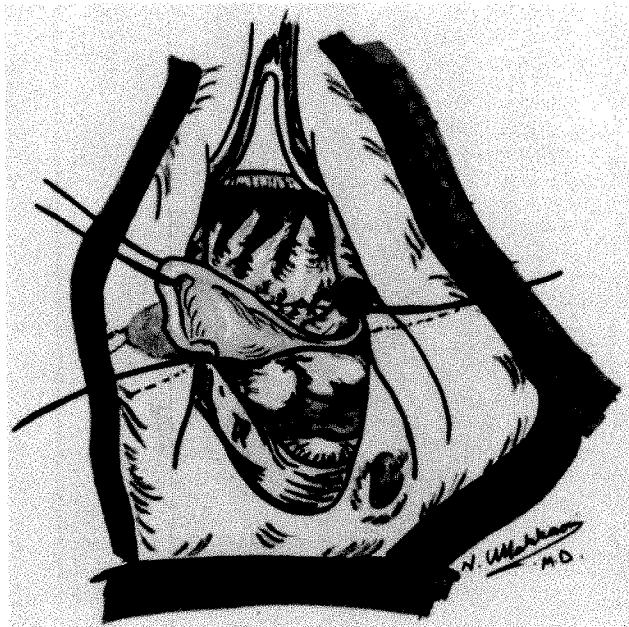


Fig 2. Two-patch repair of atrioventricular canal. Black circle indicates the area of penetrating bundle, which is avoided.

Heart Block

In this series most patients were in sinus rhythm immediately after operation or returned to sinus from junctional rhythm within the first week. Seventeen patients remained in junctional rhythm with stable hemodynamics. Complete heart block necessitating placement of a permanent pacemaker developed in only 1 patient. To eliminate the risk of damage to the conduction tissue at operation, the bare area of the ventricular crest is consciously avoided, especially underneath the inferior bridging leaflet at its insertion, which is the position of the penetrating bundle. No suture is placed here, and when this point is reached while attaching the ventricular patch, a deliberate "jump" is made into the fibrous tissue of the valve annulus. By placing tension on this continuous suture, the Dacron patch is crimped under the posterior leaflet, thereby eliminating any risk of residual ventricular septal defect. The coronary sinus is retained in the right atrium as the suture line of the atrial patch is placed on the left side of the sinus (Fig 2).

Left Ventricular Outflow Tract Obstruction

Because of the deficiency of atrioventricular septum, the left ventricular outflow tract is malformed. Therefore, potential for left ventricular outflow tract obstruction exists in the majority of hearts with AV canal defects [18, 19]. Before repair, the geometry of the AV valve is tested by injecting saline solution into the left ventricle. By using two separate patches, the height of anchorage of the mitral valve to the ventricular patch at the level of the superior bridging leaflet can be accurately judged and this potential complication avoided. In those defects where the superior bridging leaflet is tethered to the crest of the septum with short chordae, the risk of left ventricular

outflow tract obstruction is increased, as emphasized by Chang and Becker [19]. We have encountered this situation in four hearts and have divided the tethered chords to obtain exposure of the subaortic area, which was enlarged by placement of the ventricular patch to avoid this complication.

Staged Repair

Our policy has been to perform pulmonary artery banding and ligation of patent ductus arteriosus in smaller infants, less than 5 kg in body weight (36 patients), who were in intractable heart failure and in patients who were not otherwise suitable to undergo primary repair, eg, patients who belong to the Jehovah's Witness faith with low hemoglobin. The mortality after complete repair in this subset of patients was 8%. Previous pulmonary artery banding was not an incremental risk factor for mortality. In this series, 36 of 104 patients have undergone pulmonary artery banding with ligation of patent ductus arteriosus when present, without any mortality. This experience is similar to the experience of other observers [20-22]. Furthermore, in the past, the examination by one of us (S.S.) of nonsurgical autopsy specimens of hearts with complete AV canal from infants less than 3 months of age showed that the valve tissue is friable, thin, and diaphanous, hence not well suited for repair. We therefore continue to offer pulmonary artery banding to symptomatic infants less than 3 months of age.

Pulmonary Vascular Obstructive Disease

In our early experience, 3 patients died of grade IV pulmonary vascular obstructive disease. This degree of pulmonary vascular obstructive disease was not anticipated because of inadequate preoperative evaluation. These patients were all older than 1 year of age at repair and had not been banded. Lung biopsy in older patients with questionable operability may help in selection for repair. Younger age at primary repair has not been a risk factor for death or reoperation in this series. Twenty-one patients less than 1 year of age had an operative mortality of 4.7%, 42 patients between 1 and 2 years had an operative mortality of 14%, and 41 patients older than 2 years had an operative mortality of 9.7%. Newfeld and associates [23] reported the incidence of advanced pulmonary vascular obstructive disease during the first year of life in patients with complete AV canal defect and noted intimal fibrosis (grade 3 changes) between age 6 months to 1 year. Whenever feasible, primary repair should be carried out earlier, preferably by 6 months of age, before the onset of pulmonary vascular obstructive disease.

Follow-up data showed that severe mitral regurgitation did not develop in the survivors. We believe that the use of two separate patches maintaining the continuity of mitral and tricuspid components, accurate reconstruction of a trileaflet mitral valve, and suspending the valve at an appropriate height eliminate potential complications of left ventricular outflow tract obstruction and patch dehiscence. The event-free actuarial survival was 92%; the events considered were reoperation and complete heart block (Fig 3). This compares favorably with other recent

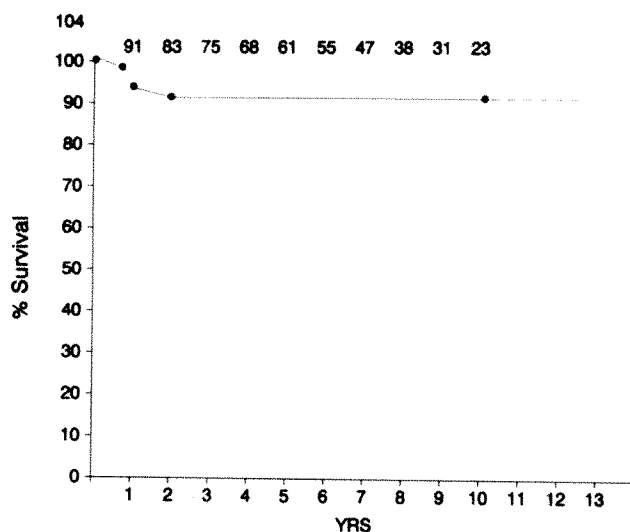


Fig 3. Actuarial event-free survival (numbers of patients at risk are above the survival line).

reports showing a higher incidence of reoperation and heart block [4, 24].

Summary

In summary, the intermediate-term result of the two-patch repair of AV canal has been satisfactory. This technique has the advantage of preserving valve tissues and valve integrity, providing durable mitral valve competence with rare dehiscence, reoperation, or heart block even in younger children.

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DISCUSSION

MR JAROSLAV F. STARK (London, England): I enjoyed your presentation. I would like you to clarify your statement about preserving the valve tissue and chordae. Do you refer to the anterior leaflet only or do you always preserve all valve tissue and all chordae to both the anterior and posterior leaflets? Professor Carpentier, when he originally described the technique, mentioned that division of some secondary and tertiary

chordae to the posterior leaflet is often necessary. We ourselves often divide some chordae to the posterior leaflet when there are short and dense chordae under the posterior leaflet to obtain better exposure and avoid the conduction mechanism.

My second comment is about keeping the left-sided AV valve as a tricuspid valve. Since we started using this technique we had to reoperate on several children who at the time of the operation

had a competent valve, did very well in the immediate postoperative period, but a few years later came in with severe left-sided AV valve incompetence. At the time of reoperation the incompetence was through the septal commissure (cleft). Closing the commissure (cleft) completely cured the problem. Currently we always close the septal commissure with interrupted stitches pledgeted with pericardial pledgets but make sure that we do not cause left-sided AV valve stenosis. I believe that this is the current practice of many congenital heart surgeons.

DR ASHRAF: In this series the chordae and the leaflet tissue were not divided, for both the anterior and posterior leaflets. The needles were passed back and forth to attach the ventricular patch. The only time any chordae were divided was at the superior bridging leaflet when the chordae were tethered and the subaortic area could not be visualized properly. Those were the only few occasions in which the tethered chordae were divided.

To answer your second question, before closing the atrial patch, we test the mitral valve by injecting saline solution into the left ventricle; if the cleft appears to be the cause, we progressively put in interrupted stitches, and see how competency is achieved. Of 104 patients, only 11 patients required closure of the cleft; 93 patients did not require closure of cleft, and we had only two reoperations with a 13-year follow-up.

DR JOSEPH J. AMATO (New Hyde Park, NY): Doctor Ashraf, I enjoyed your presentation. Just to clarify, preoperatively you showed that there were 21 patients with moderate incompetence.

Are you saying that in those 21 patients with moderate valvular incompetence these mitral valves became competent without placing sutures in the mitral leaflets? We usually repair the valve, as Mr Stark previously mentioned, not completely in most all of our patients. Did you have some incompetence in those 21 patients without suture repair?

DR ASHRAF: No, we did not. The competence of the valve was tested in the operating room, and until full competence was achieved, the operation was not over. It required a few more stitches, but hardly ever complete closure. Only 11 patients required full closure of the cleft.

DR AMATO: Doctor Ashraf, I believe you previously pointed out that you only had to put a few stitches in only a few patients. I just cannot see how the 21 incompetent valves in these patients could become competent without adding some sutures.

DR ASHRAF: Once the AV valve is supported between the patches, it does become competent.

DR JOHN W. HAMMON, JR (Winston-Salem, NC): This issue appears to be one that is being discussed a fair amount. I would like to take a straw vote. Those surgeons here who do AV canal surgery, if you routinely or almost routinely repair the so-called cleft, raise your hand; if you do not routinely repair the cleft, raise your hand. It appears that the repairers are in the majority, and perhaps discussions like this may help clarify this issue.

Double-Lung Transplantation in Children: A Report of 20 Cases

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Jean Camboulives, MD, Laurent Viard, MD, Michel Carcassonne, MD,
Roger Giudicelli, MD, Michel Noirclerc, MD, and the Joint Marseille-Montréal Lung
Transplant Program

Hôpital Ste. Marguerite, Marseille, France; La Timone Children's Hospital, Marseille, France; and Montréal Général Hospital,
Montréal, Québec, Canada

In the last 3½ years, we have performed 20 double-lung transplantations in children between 7 and 16 years old (mean age, 13 years). One patient had primitive bronchiolitis obliterans and the other 19, cystic fibrosis. Eight patients were operated on in an emergency situation, 7 of them requiring ventilator support before transplantation. The procedures were en bloc double-lung transplantation in the first 11 patients with separate bronchial anastomoses in 10, and sequential bilateral lung transplantation in the later 9 patients. There were no operative deaths. Two patients died in the hospital on postopera-

tive days 37 and 73, and there were four late deaths, which were due to infection, rejection, and bronchiolitis obliterans. The acceptable incidence of airway complications, the improvement in lung function of survivors, and the acceptable midterm survival make double-lung transplantation an acceptable alternative to heart-lung transplantation in children. However, in very small children, heart-lung transplantation may be preferable because of the size of the airway anastomoses at risk.

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The technique of bilateral lung transplantation has evolved from en bloc heart-lung transplantation to en bloc double-lung transplantation and finally to sequential bilateral lung transplantation. Although heart-lung transplantation originally was advocated for all types of parenchymal diseases and for pulmonary vascular disease either isolated or caused by Eisenmenger syndrome, it has now been restricted to irreparable or irreversible heart defects associated with pulmonary disease. Single-lung transplantation is now advocated for many parenchymal and pulmonary vascular diseases, and double-lung transplantation is advocated when both lungs have to be removed, in particular for septic lung diseases such as cystic fibrosis or bronchiectasis.

Lung transplantation has been done mostly in adult patients. The difficulty of looking after children with end-stage heart or lung disease and the uncertainty about the long-term outcome of the allografts have raised doubts about the usefulness of performing lung transplantation in children. It has been suggested [1] that children will experience more episodes of rejection, both acute and chronic, which will result in graft attrition and a disappointing long-term outcome. In the world experience, heart-lung transplantation has been by far the most frequent procedure reported for lung transplantation in children [2] and in patients with cystic fibrosis in particular [3]. In 1988 in Marseille, we started a double-lung transplant program in children with cystic fibrosis [4].

This article reports our experience and our intermediate-term results in 20 consecutive pediatric patients undergoing double-lung transplantation in the combined Marseille-Montréal lung transplant program.

Material and Methods

Between May 1988 and December 1991, 58 children were accepted for transplantation, including some very severely ill patients who required ventilation. Few children (only 3) were denied inclusion on the waiting list. Twenty-two patients (40%, 22/55) died while awaiting transplantation because of a lack of donors. During the same period, 20 patients underwent bilateral lung transplantation.

There were 11 girls and 9 boys. The average age at transplantation was 13 years (range, 7 to 16 years). The average weight was 25 kg (range, 14 to 56 kg). The indication for transplantation was cystic fibrosis in 19 patients and primitive bronchiolitis obliterans in 1 patient.

The nutritional status of most patients was poor, their growth pattern being well under the normal range for their age. Twelve patients were in stable condition and 8, in severe condition at transplantation. These 8 patients were in intensive care and receiving intravenous inotropic support necessitated by secondary right ventricular failure; 7 of them were on a ventilator with nasotracheal intubation for 1 day to 21 days before transplantation. The patient having ventilator support for 21 days had a tracheostomy 3 days before transplantation.

Age of the donors ranged between 4 and 20 years (mean age, 11 years), and weight ranged between 17 and 70 kg (mean weight, 37 kg). After the first few patients, little

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attention was paid to size and weight matching between donor and recipient, and more attention was given to the size of the chest. The criterion used for size matching was the circumference of the thorax at the nipple level, a variation of 10% being accepted.

The lungs were procured as part of a multiorgan harvesting, the technique including crystalloid cardioplegia and a single flush of 4°C Euro-Collins solution in the pulmonary artery after an infusion of prostaglandin E₁. The ischemic time ranged from 2 hours 15 minutes to 7 hours (mean time, 4 hours $\pm$ 1 hour 30 minutes). In the first 11 patients, the en bloc double technique [5] was used with a tracheal anastomosis in the first patient and bilateral bronchial anastomoses in the following 10 patients [6, 7]. In the last 9 patients, bilateral single-lung transplantation [8] was performed through a bilateral transverse thoracotomy. In none of the patients was omentopexy or any wrapping of the airway anastomoses done. All operations were performed with cardiopulmonary bypass, moderate hypothermia, and a beating heart except during the left atrial anastomosis in en bloc double-lung transplantation, where cardioplegia was used.

The immunosuppression regimen included induction with rabbit antithymocyte globulin (2.5 mg/kg) for 7 to 14 days and triple immunosuppression with cyclosporin A, azathioprine, and corticosteroids. Cyclosporin A was given preoperatively, intraoperatively, and postoperatively as a continuous intravenous administration until oral administration became possible after approximately 2 weeks. We aimed at a residual level of 150 to 250 ng in serum or 300 to 500 ng in total blood. The steroids were given intraoperatively (4 ng $\cdot$ kg⁻¹ $\cdot$ d⁻¹) and withheld thereafter for 2 to 3 weeks in the initial experience. In the last 7 patients, corticosteroid administration was started earlier at 0.6 mg/kg and tapered to 0.2 mg/kg after 4 to 6 months. Azathioprine was given at 2 mg/kg for the first week and then reduced to 0.5 to 1.5 mg/kg to obtain a white blood cell count in the range of 4,000 to 7,000/ μ L (4.0 to 7.0 $\times$ 10⁹/L).

The postoperative antibiotic regimen included a double or triple association to obtain synergy and was usually identical to the pretransplantation treatment. The antibiotics commonly used, based on the most recent assessment of bacterial sensitivity in vitro, were a penicillin (ceftazidime, imipenem), an aminoglycoside (amikacin sulfate, tobramycin sulfate), and a quinolone (ciprofloxacin). Antifungal prophylaxis was also instituted for 1 month (amphotericin A, 0.2 mg/kg). Rejection monitoring included routine endoscopies and biopsies, the former being started after day 5 for inspection of the airway anastomoses. Biopsies were done systematically every week, then every month after the second month, and then every 3 months in the following year. Subsequently, routine lung function studies, computed tomographic scans, and scintigraphs were performed. Rejection episodes were treated with intravenous pulse steroid therapy (17 mg $\cdot$ kg⁻¹ $\cdot$ d⁻¹) and OKT3 when resistant to steroids. Four episodes of rejection were treated with OKT3.

Results

There were no operative deaths and two in-hospital deaths. One involved a 12-year-old patient with severe multiorgan failure preoperatively (coma, renal failure, artificial ventilation). This patient died on postoperative day 37 of multiorgan failure, infection, airway dehiscence, and cerebral anoxia. The other patient died of posttransplantation lymphoproliferative lung disease 73 days after transplantation. This patient had multiple episodes of rejection requiring augmentation of immunosuppression and repeated pulse steroid therapy. He also had one course of OKT3.

There were four late deaths. One patient with cystic fibrosis but otherwise in excellent condition died of acute bronchopneumonia 4 months after sequential bilateral lung transplantation. The causative organism was unknown, as the death occurred in a remote community hospital where no bacterial investigation was done. The other three deaths were due to bronchiolitis obliterans at 1 year, 1 year 3 months, and 1 year 6 months. In 2 of these patients, it was associated with chronic infection and repeated episodes of rejection. Both patients also had a permanent left main bronchial stent.

The postoperative course was difficult, with most patients requiring mechanical ventilation for 1 day to 54 days (mean duration, 16 days). Eight patients needed a temporary tracheostomy. The duration of ventilator support after transplantation did not correlate with the time of ischemia or the need for preoperative ventilation. Four patients had renal failure requiring peritoneal dialysis. Patients had insulin-dependent diabetes, discovered during a pulse of intravenous steroid therapy. Two patients had a temporary unilateral diaphragmatic palsy. Cardiac function, even when impaired preoperatively, always improved. Fifteen patients required prolonged inotropic support after transplantation until the right ventricle recovered normal function.

Postoperative Infections

The duration of the initial course of antibiotics ranged from 10 to 35 days based on the negativity of bronchial secretions. Pulmonary infections caused by *Pseudomonas aeruginosa* developed in 5 patients during their initial hospital course. No patient died of this infection, but in 2 it became chronic, associated with bronchiolitis obliterans, and the patients died at 13 and 19 months.

A late infection developed in 6 patients. One of them died at 4 months. A *Pseudomonas aeruginosa* infection developed in 5 patients, 2 of whom were cured. In the other 3, the infection was chronic and recurrent. A cytomegalovirus lung infection developed in 5 patients and was diagnosed by bronchoalveolar lavage (4 patients) or by transbronchial biopsy (1 patient). All were successfully treated by DHPG.

Airway Complications

Bronchoscopy under short general anesthesia, at bedside when necessary, was well tolerated and uneventful. The patient with a tracheal anastomosis had development of an anastomotic stricture 3 months after transplantation. This was treated with one session of laser therapy. Nine-

teen patients had 38 bronchial anastomoses at risk. Twelve patients had simple or uneventful healing, whereas 7 had airway complications. One patient had bilateral necrosis and dehiscence (the patient who died 37 days after transplantation). Two patients had bilateral bronchomalacia, predominant on the left side, and needed a permanent left main bronchial stent. Both later died of bronchiolitis obliterans and superimposed rejection and infection.

Left main bronchomalacia developed in 4 patients, necessitating one permanent and three temporary endobronchial stents. All stents were the Dumon Silastic (Dow Corning, Midland, MI) stents [9]. In the initial experience, bronchial complications were found to be related to preoperative ventilation and younger age of recipients (less than 10 years). In the recent experience, and particularly with sequential bilateral lung transplantation, bronchial healing was generally uneventful.

Rejection Episodes

In the first month, 16 patients had one or two rejection episodes (0.9 episode per patient). At 1 year, rejection occurred at the rate of 0.2 rejection episodes per patient. After 1 year, there were no acute rejection episodes.

Bronchiolitis Obliterans

Bronchiolitis obliterans developed in 6 of 14 patients followed up for more than 6 months, an incidence of 42.9%. This diagnosis was based on a progressive, irreversible decline in pulmonary flow measurements. Histologic diagnosis was accomplished in 3 patients by transbronchial biopsy and in 3 by open lung biopsy. Three of the 6 died of infectious complications secondary to bronchiolitis obliterans. One patient underwent retransplantation after a year. Before the heart-lung retransplantation, he received ventilator support for 66 days. One year after retransplantation, he is in excellent condition. Two patients are awaiting retransplantation 2½ years after initial double-lung transplantation. Eight patients are leading a normal life, but 2 of them are considered to have moderate and stable bronchiolitis obliterans.

Lung Function

After transplantation, there was significant improvement in forced expiratory volume in 1 second from $25.5\% \pm 2.1\%$ predicted before transplantation to $75\% \pm 5.8\%$ predicted at 3 months, $95.3\% \pm 7.4\%$ predicted at 6 months, and $87.4\% \pm 10.8\%$ predicted at 1 year ($p > 0.01$ compared with pretransplantation values for all three periods) (Fig 1). The mild decline observed at 1 year is related to the development of bronchiolitis obliterans in 3 patients. Similarly, the forced vital capacity increased significantly from $41.4\% \pm 2.3\%$ predicted before transplantation to $84.5\% \pm 4.8\%$ predicted at 3 months, $101.2\% \pm 4.8\%$ predicted at 6 months, and $99.1\% \pm 9.2\%$ predicted at 1 year ($p < 0.01$ compared with pretransplantation value) (see Fig 1).

Follow-up

Overall, 13 patients, including 1 patient who underwent retransplantation, are doing well or reasonably well 3 to

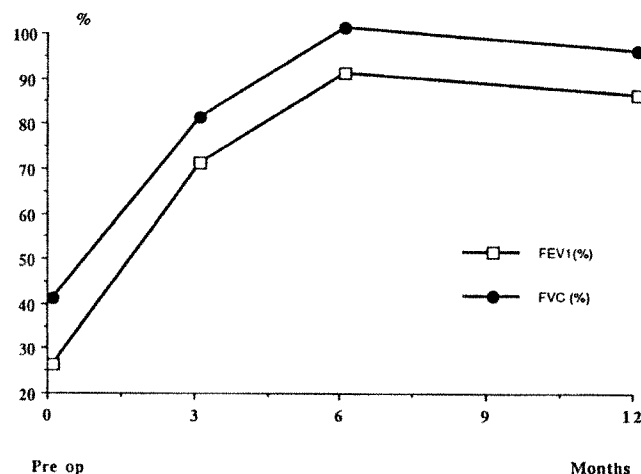


Fig 1. Changes in lung function during the first year after operation. Data are shown as percent predicted. (FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity.)

45 months after transplantation, this including the patient with retransplantation. The actuarial survival is 70% at 3 years (Fig 2). Nine of the 13 have resumed a normal life with considerable development and weight gain. They attend school, and some have taken up hobbies or sports requiring a high level of activity such as alpine skiing, tennis, soccer, or gymnastics.

Comment

The recent success of isolated lung transplantation reported by the Toronto group was followed by an explosion in the number of transplantations performed worldwide. Current registry data [2] indicate that as a consequence of the increase in the number of single- and double-lung transplantations performed, heart-lung transplantation has dwindled. Although single-lung transplantation can be suitable therapy for patients with nonseptic parenchymal or vascular lung disease, replacement of both lungs is thought to be essential for any patient with evidence of pulmonary infection. Contrary to the experience in adults, initial reports on pediatric lung transplantation have not been encouraging, with mortality attributed to a high incidence of acute rejection, airway complications, and infections [1].

In this series, we report our experience with bilateral lung transplantation in children less than 17 years of age. Bilateral lung transplantation without the heart was performed as the primary graft in all patients with parenchymal disease and a normal heart or a temporarily failing heart. The relatively low morbidity observed in this pediatric lung transplant experience may reflect the fact that children are generally more tolerant of surgical complications and the fact that the bacteria they harbor have not necessarily acquired the multiresistance to antibiotics observed in the adult population with cystic fibrosis. In addition, the absence of operative mortality in this pediatric group, which consists almost exclusively of patients with cystic fibrosis, may reflect the lack of extensive

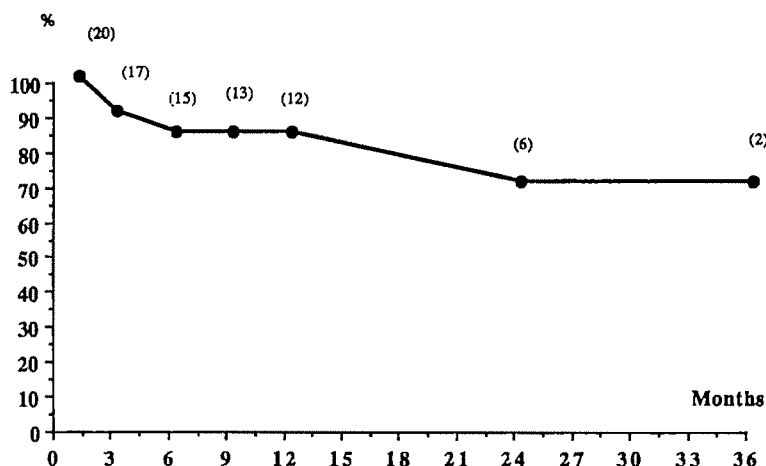


Fig 2. Actuarial survival curve for 20 children undergoing double-lung transplantation. Number of patients at risk is in parentheses.

thoracic adhesions and hence the reduced bleeding and the lower cardiopulmonary bypass time compared with adults. Heart-lung transplantation was used as the second procedure for a recipient of a double-lung transplant in whom bronchiolitis obliterans developed. The choice of a heart-lung transplant rather than a redo double-lung transplant was made because the patient had had en bloc double-lung transplantation, and we did not wish to leave segments of bronchus from 2 donors.

During the first 6 months, pediatric recipients of lung transplants appeared to experience the same complications seen in adults. Infection, rejection, and airway complications are not uncommon. Our methods of surveillance and investigation of pulmonary complications are no different from those in adult patients. We use fiberoptic bronchoscopy liberally when indicated. Transbronchial biopsy and bronchoalveolar lavage are routinely used at the time of bronchoscopy to rule out rejection or infection.

Children are at the highest risk of the development of bronchopneumonia during the first month after transplantation. In this series, five episodes were observed to occur in the first month in 20 patients at risk. In the subsequent 6 months, only three episodes were noted in 14 patients at risk. These data suggest that as the incidence of rejection decreases and the doses of immunosuppression are lowered, and the patient is away from the hospital environment, the risks of infection decrease.

Pediatric recipients of lung transplantation are also at highest risk of development of acute rejection during the first months. We noted 18 episodes in 20 patients at risk during this period. This is no different from the experience observed in other pediatric organ transplant programs or in adult patients [10]. All episodes of rejection except for three were responsive to pulse steroid therapy. OKT3 was effective in treating steroid-resistant rejection on three occasions. In 1 child who received relatively high and repeated doses of steroid therapy for the treatment of rejection posttransplantation lymphoproliferative disorder developed and the patient died 73 days after transplantation. This 5% incidence of lymphoproliferative disorder is similar to that reported in adult patients [11].

The frequency and severity of airway complications were within normal limits and have decreased substantially in the more recent experience with the bilateral single-lung technique. We therefore believe that airway complications are no different in children than they are in adults. Although our numbers are too small to confirm such an observation statistically, we believe that younger children should be considered for a tracheal anastomosis rather than bronchial anastomoses. The age and weight of this group are not defined. Whether this is incorporated as part of a heart-lung or double-lung procedure remains to be determined. More recently, we have performed a successful heart-lung transplantation in a 6-year-old boy weighing 12 kg with cystic fibrosis (not included in this study) and employed a tracheal anastomosis for this small patient.

Pulmonary function testing in our pediatric lung transplant series indicates significant improvement in forced expiratory volume in 1 second and forced vital capacity immediately after transplantation. There is continual improvement up to 6 months after operation, at which point lung volumes start to plateau. A slight drop in the percent predicted forced expiratory volume in 1 second and forced vital capacity observed at 1 year in our series may reflect the development of bronchiolitis obliterans in some patients. These objective findings indicate that bilateral lung transplantation in the pediatric population results in improvement in lung function and hence an expected better overall performance by these children.

Among the 14 patients followed up for longer than 6 months, bronchiolitis obliterans developed in 6. We believe this incidence is no different from what can be expected in adults with our current methods of immunosuppression: cyclosporine, azathioprine, and low doses of prednisone. Three of the 6 patients are in stable condition with no further drop in forced expiratory volume in 1 second and are now studying and working full time. Two other patients with marked dyspnea and limited function are awaiting transplantation. The only patient in this series who has had retransplantation has regained normal function and is symptom-free 9 months after receiving a heart-lung transplant. Whether retransplantation should

be considered for patients with development of bronchiolitis obliterans in the primary grafts and which technique of retransplantation to use are controversial. As most patients with end-stage bronchiolitis obliterans will harbor fungal or bacterial infection, it is almost certain they would require replacement of both lungs. Whether heart-lung or double-lung retransplantation is chosen will likely be addressed in the next few years as more patients with bronchiolitis obliterans are seen for retransplantation.

The issue of the growth potential of transplanted lung allografts in children is not resolved. There is, however, experimental evidence to suggest that lung allografts show an increase in airway diameter and lung volumes with age [12]. Hislop and associates [13] reported an increase in both number and size of alveoli after allogeneic single-lung transplantation in animals. Whether growth potential differences between donor and recipient bronchi will occur and lead to the risk of anastomotic stenosis must still be determined. Within the limited period of observation in this study, we can report normal clinical and radiologic thoracic development and the absence of airway complications, findings attributed to the development of donor lungs.

Finally, the results in the severely diseased patients needing artificial ventilation and inotropic support before transplantation were not different from those in the other patients. This was true with reference to all variables, such as survival, complications, and difficulty of postoperative management. Therefore, we believe that mechanical ventilation per se before transplantation should not be considered a contraindication to transplantation. Multi-organ failure before transplantation, however, is a definite contraindication, and our patient who died on day 37 would not have been a candidate now for transplantation.

We conclude from this study that bilateral lung transplantation is a valid option for the treatment of children with end-stage lung disease. Currently, sequential bilateral lung transplantation is our procedure of choice in all patients with septic lung disease. Heart-lung transplantation is rarely needed and should be restricted to patients with combined heart and lung disease or when bronchial anastomoses are likely to be at risk for the development of complications, as in retransplantation and in younger children with smaller airways. Although pediatric bilateral lung transplantation can result in good intermediate-term survival and function, research directed toward prevention and treatment of bronchiolitis obliterans is needed to achieve better long-term survival.

Addendum

Since this report was written, 2 patients have undergone retransplantation for bronchiolitis obliterans 2 and 2½ years after double-lung transplantation. Both had heart-lung transplantation and died after operation. One died of an oversized graft and 1 of inability of the heart to resume normal function. The second patient was in multiorgan failure while on the ventilator for 4 weeks and had severe metabolic disturbances that may have caused the failure of an otherwise uneventful operation. Since then, a 14-year-old patient has had a successful sequential bilateral lung transplantation for cystic fibrosis. We have therefore updated the actuarial survival curve (Fig 3).

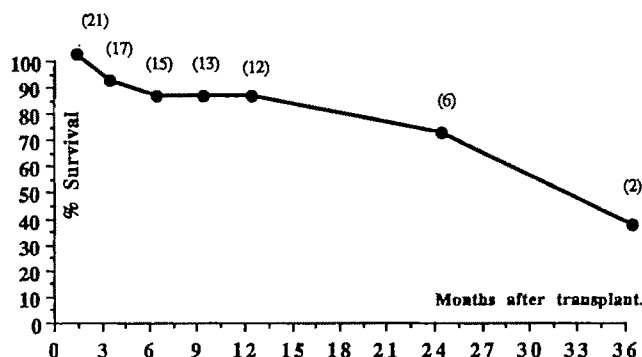


Fig 3. Updated actuarial survival curve for 21 children undergoing double-lung transplantation. This curve represents that in Figure 2 revised after two unsuccessful retransplantations. The low survival rate at 3 years may not be significant because of the small number of patients at risk. Number of patients at risk is in parentheses.

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DISCUSSION

DR R. MORTON BOLMAN III (Minneapolis, MN): I enjoyed your presentation very much, Dr Métras. My colleagues and I have also had some experience with retransplantation in children. In children with cystic fibrosis in whom obliterative bronchiolitis develops, is single-lung retransplantation adequate, or, in the likelihood of bronchiectasis and infection developing in the contralateral lung, would bilateral replacement be better? I notice you did a heart-lung transplantation in 1 child. Why did you do that?

DR MÉTRAS: In our experience, all these patients with cystic fibrosis have chronic infection, and we would not recommend single-lung transplantation. The problem is we do not know yet what to do—another sequential bilateral lung transplantation or a heart-lung transplantation. This is, of course, debatable.

As for the patient who underwent heart-lung transplantation, we chose that procedure because the first operation was a double-lung transplantation by the technique of Dr Cooper. We did not want the patient to have bronchus from 3 people, 1 recipient and 2 donors, so we decided to do heart-lung transplantation.

DR DONALD C. WATSON JR (Memphis, TN): I enjoyed your presentation very much. It reminds me of why people often go into cardiothoracic surgery, that is, to take basic and clinical research to solve new or difficult problems. You mentioned a limited donor supply, as did Dr Spray yesterday. I have one observation and two questions.

About 2 years ago, my associates and I were asked to evaluate a 4½-year-old girl with primary pulmonary hypertension. She ultimately was put on the recipient list. She waited until the parents asked, "Why wait? We can help." Ten months ago, her mother donated a right lower lobe, and today that young girl is out of the hospital and back in school after a complicated course and recovery from a lymphoproliferative disease related to Epstein-Barr virus.

This isolated case was pushed by circumstances, but the pediatric patient does present some unique options. My two questions are the following: (1) Do you think that lung donation from a living relative is a real option, not necessarily for our particular scenario but for patients with cystic fibrosis? and (2) Will the type of scenario I described encourage a critical review of the organ donation base that we currently use?

DR MÉTRAS: I think the shortage of donors favors bilateral lung transplantation in patients with cystic fibrosis instead of heart-lung transplantation. In France, the demand for hearts is so great that it is very difficult to find a heart-lung donor. However, once the heart has been donated, obtaining the lungs is relatively easy. I think the tendency to use bilateral lung transplantation instead of heart-lung transplantation is going to increase.

As for your lobar transplant, I think it is a very nice success and I congratulate you for your beautiful experience, but I have some doubts. I believe it would be a lifesaving procedure only for a certain time, because it has been shown that multiplication and growth of the alveoli are finished after the age of 8 years. One lobe from an adult cannot develop in a child except by emphysema, and I do not see how such a lobe can make a normal lung for a growing child. Nevertheless, I am sure that in some cases this would be a lifesaving procedure that could be followed later by replacement with a whole lung.

DR G. ALEXANDER PATTERSON (St. Louis, MO): Professor Métras, that was a beautiful presentation, and you are to be congratulated for those results, particularly considering that children with cystic fibrosis represent the overwhelming majority of your patients.

I have two questions. First, we heard yesterday from Dr Spray that their pediatric group uses cardiopulmonary bypass routinely in all cases, and you have said the same. Can you explain why you use bypass to do sequential bilateral lung transplantation in these children and whether you have encountered any difficulty because of the use of bypass?

Second, I was struck by the lack of septic complications in your patients with cystic fibrosis. What type of prophylaxis do you use? Do you treat the sinuses preoperatively, and what antibiotic regimen is used?

DR MÉTRAS: To answer your second question first, all the patients have the sinuses treated. There were, in fact, 12 patients who had complications, some of them very severe. Concerning the antibiotic regimen, I am a surgeon; the intensivists use antibiotics the names of which I do not even know, and there are always new antibiotics. In the postoperative prophylaxis three or four antibiotics are used. This is the best answer I have.

DR PATTERSON: Is it true that there was only one perioperative death resulting from sepsis?

DR MÉTRAS: The patient died, but not of sepsis. Sepsis was one of several of his problems. It is true that no patient in our experience died of postoperative infection only.

As for your first question on cardiopulmonary bypass, I am happy that you asked about this, because I think the use of cardiopulmonary bypass in the pediatric population is harmless and even useful. These children had no pleural adhesions. This is one characteristic of cystic fibrosis in children in our experience: there are very few adhesions. So cardiopulmonary bypass does not add any more risk of hemorrhage, and the recent patients bled very little postoperatively. We use cardiopulmonary bypass because most often the donor is a remote donor. At the appropriate time after a donor has been found, we put the patient on bypass, remove the two lungs, and prepare everything for the anastomoses. Then when the lungs arrive, we can rapidly perform the three anastomoses. We think this is a quicker, simpler procedure than to wait for the donor and then try to do sequential bilateral single-lung transplantation without bypass.

DR HANI SHENNIB (Montreal, Que, Canada): Perhaps I can follow up on this question. In regard to Dr Patterson's questions as to what antibiotics we use and why we do not have a high incidence of sepsis in these patients, I think it is necessary to remember that what we are dealing with in this particular study is a population of children. We tend to see a higher incidence of multiresistant *Pseudomonas* infections in adults compared with children. Most of these children would have a combination of antibiotics that would be effective. We tend to use aggressive doses of aerosolized tobramycin or Coly-Mycin in the patients with cystic fibrosis (we put almost all our patients on aerosol therapy) in addition to intravenous antibiotics based on the multisensitivity in vitro.

Retrograde Continuous Warm Blood Cardioplegia: Maintenance of Myocardial Homeostasis in Humans

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Recent clinical reports have suggested that continuous delivery of oxygenated warm blood cardioplegia through the coronary veins (retrograde cardioplegia) produces good myocardial preservation during aortic cross-clamping. No data exist, however, about actual myocardial metabolism/homeostasis during retrograde warm blood cardioplegia. We studied 100 consecutive patients undergoing coronary artery bypass grafting, aortic valve replacement, or both who received retrograde continuous warm blood cardioplegia (4:1 dilution) during aortic cross-clamping for 54 to 174 minutes. We measured pH, oxygen tension, carbon dioxide tension, HCO_3^- , base excess, and oxygen content of the inflow cardioplegia and the blood egressing from coronary arteries during each arteriotomy for bypass grafting (arteries act as postcapillary veins with retrograde cardioplegia) or the left and right coronary orifices during aortic valve replacement. We also measured these variables from the coronary sinus effluent 1 minute after release of the aortic cross-clamp. Retrograde cardioplegia flow ranged from 50 to 250 mL/min (mean flow, 150 mL/min). All patients were maintained at normothermia during bypass. A total

of 460 samples were analyzed (4.6 per patient). Neither the duration of aortic cross-clamping nor the artery sampled affected myocardial blood gases. The pH dropped from 7.41 ± 0.05 for the inflow cardioplegia to 7.32 ± 0.1 when sampled from coronary arteries, and the oxygen tension fell from 181 ± 25 to 28 ± 5 mm Hg, respectively. Carbon dioxide tension rose from 31.0 ± 4.1 to 41.4 ± 9.8 mm Hg. Coronary sinus blood gases 1 minute after cross-clamp removal showed no acidosis or oxygen debt. These results indicate that (1) myocardial homeostasis is preserved by retrograde continuous warm blood cardioplegia during normothermic aortic cross-clamping for up to 3 hours in humans; (2) normal myocardial metabolism and oxygen uptake can be maintained solely by retrograde cardioplegia in the arrested heart, eliminating oxygen debt and ischemia; and (3) unlike experimental models, the arrested human heart is *very* active metabolically. Further application of this new clinical technique appears warranted, provided appropriate monitoring is used.

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The ability of surgeons to preserve myocardial viability during periods of aortic cross-clamping has existed since the earliest days of clinical open-heart operations in the 1950s. Prompted by the laboratory successes of Blanco and associates [1], Lillehei and his colleagues [2] successfully operated on the aortic valve using continuous retrograde perfusion of the beating, warm human heart through a catheter placed in the coronary sinus. Even in 1954, the idea of perfusing oxygenated warm blood into the myocardium through the coronary veins to preserve the heart was not new, having been described as early as 1898 by Pratt [3].

By 1959, however, despite 4 years of successful clinical application, retrograde continuous warm perfusion of the heart was largely abandoned in favor of antegrade intermittent hypothermic perfusion or cardioplegia [4]. Re-

cently, owing largely to improved delivery systems and the recognition of the consequences of myocardial ischemia such as reperfusion injury, retrograde continuous warm perfusion of the heart has been reintroduced into the clinical arena [5, 6]. Despite several reports on the successful human application of this technique, little experimental or clinical work is available that describes the effectiveness of this technique in preventing myocardial ischemia.

To understand how continuous retrograde perfusion of oxygenated blood cardioplegia might preserve myocardial viability, the interrelationship of the coronary venous and arterial anatomy must be considered (Fig 1). The coronary venous system not only connects with myocardial capillaries but also interconnects with other coronary veins by way of veno-venous collaterals and with the ventricular and atrial cavities directly through the thebesian vessels. So rich are these venous connections that only 25% of blood retroinfused into the coronary sinus traverses the capillaries, the remainder exiting the myocardium through the venous channels without providing nutrient

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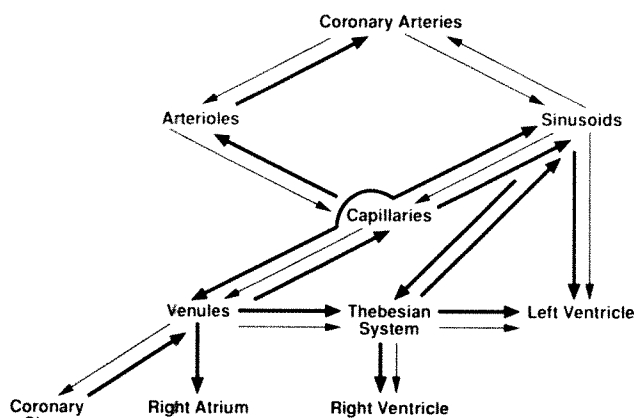


Fig 1. Coronary venous and arterial drainage patterns. Dark arrows show retroperfused blood flow patterns.

blood flow [7]. The retroperfused blood cardioplegia that does traverse the capillaries, in general, uses the coronary arteries to egress from the myocardium. Thus, in continuous retrograde cardioplegia, sampling the coronary artery effluent would be expected to give a most reliable measure of myocardial oxygen extraction, acid-base status, and homeostasis. The testing of this hypothesis in 100 consecutive patients undergoing myocardial revascularization, valve replacement, or both forms the basis of this report.

Material and Methods

The study comprises all adult patients having myocardial revascularization, valve replacement or repair, or a combination of these from February 1991 to the present on the service of the primary author (S.R.G.). Myocardial protection was provided by continuous retrograde infusion of warm (37°C) blood cardioplegia (4:1 dilution) administered through a flexible catheter with a manually inflated distal balloon and with constant monitoring of coronary sinus pressure (Gundry RSCP catheter; DLP, Inc, Grand Rapids, MI). The technique of insertion of this catheter has been previously described [8]. Essentially, it entails placing the catheter into the coronary sinus through a pursestring suture in the high right atrium and directing the catheter using a flexible stylet.

Induction of myocardial arrest was accomplished by the infusion of warm blood cardioplegia (4:1 dilution) at 250 to 300 mL/min using a final KCl concentration of 27 mEq/L into the coronary sinus RSCP catheter until arrest was achieved and then switching to continuous infusion of a 4:1 blood cardioplegia mixture with a KCl concentration of 9 mEq/L at 110 to 150 mL/min. Whenever a coronary arterial blood gas analysis showed a pH of less than 7.30, cardioplegia flow was increased by 50 mL/min up to 300 mL/min. Assessment of myocardial perfusion was made visually by noting engorged red veins and blue arteries and by noting the issuance of dark blood from arteriotomies or coronary orifices; also, a low-pressure alarm was placed on the coronary sinus pressure line (DLP, Inc) and set to sound when coronary sinus pressure was less than 15 mm Hg.

Samples for blood gas analysis were taken from the inflow cardioplegia line and from each coronary arteriotomy at the time of bypass graft placement, and from the coronary artery ostia in the case of aortic valve replacement. They were repeated at least every half hour. At the termination of aortic cross-clamping, cardioplegia infusion was stopped and the balloon deflated. One minute later, a final blood gas sample was taken from the coronary sinus through the retrograde catheter, which was still in place, and compared with a blood gas sample taken from the arterial line from the bypass pump. All blood gas samples were analyzed for pH, oxygen tension (P_{O_2}), carbon dioxide tension (P_{CO_2}), HCO_3^- , base excess, and oxygen content. Comparison was made between the inflow cardioplegia and the blood egressing from the coronary arteries as a measure of myocardial metabolism and between the inflow cardioplegia and the coronary sinus blood after release of the cross-clamp as a measure of oxygen debt. All patients were maintained at 37°C during sampling.

Results

The results of the blood gas analyses for the first 100 patients studied are shown in Table 1. A total of 460 samples were analyzed (4.6 ± 1 samples per patient). The inflow cardioplegia reflected a 4:1 mixture of perfusion blood and Roe's solution, which supposedly had been buffered to a pH of 7.45 before delivery to the operating room but was consistently slightly acidotic on delivery (base excess -3.7 ± 2.6 and pH 7.41 ± 0.05). Blood gases from the coronary artery effluent, representing blood that had traversed the myocardial capillaries, had a mean pH of 7.32 ± 0.1 with a base excess of -4.7 ± 2.6 . Postcapillary pH ranged from a low of 7.20 to a high of 7.55. Coronary sinus blood pH after cross-clamp release was 7.38 ± 0.1 with a base excess of -0.4 ± 3.0 versus a pH of 7.42 ± 0.08 in the arterial line.

The P_{O_2} of the inflow cardioplegia was 181 ± 25 mm Hg, which fell to 28 ± 5 mm Hg when measured in the coronary artery effluent. This value rose to 37 ± 6 mm Hg when measured in the coronary sinus after

Table 1. Summary of Blood Gas Analyses^a

Variable	Cardioplegia	Coronary Artery Effluent	Coronary Sinus 1 Minute After ACC Release
pH	7.41 ± 0.05	7.32 ± 0.1	7.38 ± 0.1
P_{O_2} (mm Hg)	181 ± 25	28 ± 5	37 ± 6
P_{CO_2} (mm Hg)	31.0 ± 4.1	41.4 ± 9.8	40.5 ± 4.5
HCO_3^-	19.3 ± 1.5	20.5 ± 1.8	23.1 ± 1.9
Base excess	-3.7 ± 2.6	-4.7 ± 2.6	-0.4 ± 3.0
O_2 content	7 ± 2	4 ± 2	5 ± 2

^a Data are shown as the mean $\pm$ the standard error of the mean.

ACC = aortic cross-clamp; O_2 = oxygen; P_{CO_2} = carbon dioxide tension; P_{O_2} = oxygen tension.

cross-clamp release versus 180 ± 21 mm Hg systemically. The P_{CO_2} of the inflow cardioplegia was 31.0 ± 4.1 mm Hg and rose to 41.4 ± 9.8 mm Hg in the coronary artery samples, similar to the value of 40.5 ± 4.5 mm Hg measured in the coronary sinus later. Little change in bicarbonate ion was detected, which increased from 19.3 ± 1.5 (inflow) to 20.5 ± 1.8 (postcapillary outflow) and measured 23.1 ± 1.9 in the coronary sinus after unclamping. Oxygen content of the inflow cardioplegia was 7 ± 2 , which decreased to 4 ± 2 in the coronary artery effluent, a value similar to that for the coronary sinus blood.

Cross-clamp times ranged from 54 to 174 minutes. No difference in blood gases could be detected based on duration of cross-clamping. Nor could a relationship be found in myocardial blood gases based on the region of the heart served by a coronary artery, although the right coronary and posterior descending coronary arteries had slightly lower pHs and PO_2 s than other regions.

In several hearts, notably those with hypertrophy, postcapillary blood pH appeared to correlate directly with cardioplegia flow. As an example, take the case of a 76-year-old man with left ventricular hypertrophy who was undergoing a bypass procedure. The initial blood gas analysis of the inflow cardioplegia showed a pH of 7.40, P_{CO_2} of 31 mm Hg, PO_2 of 176 mm Hg, base excess of -4.5 , and oxygen content of 7.3. At a flow of 125 mL/min, the initial left anterior descending coronary artery blood had a pH of 7.20, P_{CO_2} of 53 mm Hg, PO_2 of 45 mm Hg, base excess of -6.7 , and oxygen content of 4.9. When the inflow cardioplegia rate was increased to 180 mL/min, the subsequent blood gas values in that artery changed to a pH of 7.36, P_{CO_2} of 33 mm Hg, PO_2 of 35 mm Hg, base excess of -5.6 , and oxygen content of 4.6, thus indicating normalization of pH and P_{CO_2} but a still high oxygen extraction.

When the pH of the coronary arterial blood gas fell to less than 7.30, flows were increased up to 300 mL/min until a pH of greater than 7.30 was obtained. Increased flows were required in 48 of the 100 patients.

Comment

Retrograde continuous warm (or normothermic) cardioplegia for myocardial protection during aortic cross-clamping differs little from that used by Lillehei and co-workers [2] nearly 40 years ago with the exception that potassium is now added to the perfusate to arrest the heart. This addition was made secondary to the experimental findings that most of the energy savings afforded the heart by cardioplegia come from mechanical arrest and that little additional benefit is gained by cooling [9].

Extrapolating from these experimental findings, Salerno and co-workers [6] and Lichtenstein and associates [10] clinically showed that good myocardial protection could be achieved by continuous perfusion of the heart with potassium blood cardioplegia in either an antegrade or retrograde fashion. The former, because of its complicated delivery system and the need to shut off cardioplegia or snare coronary arteries to construct anastomoses, was and remains clinically difficult to apply. However,

since our introduction in 1987 of transatrial insertion of coronary sinus catheters, facile retrograde delivery of cardioplegia makes retrograde warm cardioplegia an everyday clinical reality [8]. Whether retrograde continuous warm cardioplegia allows normal myocardial homeostasis and prevents myocardial ischemia in humans was not known heretofore. The degree of metabolic activity of the warm, arrested human heart was also unknown, despite conjecture based on animal experiments. Last, the effect of using retrograde warm cardioplegia solely without an initial antegrade dose was unknown.

The results of our study clearly indicate that the human heart is fully capable of using blood perfused retrogradely through the coronary veins to maintain myocardial homeostasis. This, in itself, is not surprising, as retrograde perfusion of oxygenated blood without cardioplegia was shown by Lillehei and colleagues [2] in 1956 to maintain myocardial viability during short periods of aortic cross-clamping. Hammond and associates [11] demonstrated in dogs similar myocardial "venous" PO_2 s to those of our patients during 1 hour of retrograde coronary sinus perfusion at 37°C in the beating heart, but they noted better functional recovery, particularly of the right ventricle, if inflow perfusion temperature was lowered to 26°C .

Our study demonstrates that blood gas measurements of blood egressing from the heart through the coronary arteries closely approximates normal coronary sinus blood gas values. What is perhaps surprising is the high degree of oxygen extraction and therefore metabolism of the arrested human heart. This is contrary to reports of myocardial metabolism in animals by Buckberg [12], Bernard [9], and their co-workers that suggest that the normothermic, arrested heart requires about 90% less oxygen than the beating, working heart. Because coronary blood flow is approximately 4% of total cardiac output, normal coronary blood flow usually is 200 to 300 mL/min. Thus, a warm, arrested heart should require only 10% of this flow or 20 to 30 mL/min to maintain homeostasis. As only 25% of retrograde perfusion through the coronary veins traverses the myocardial capillary bed, it would be proper to suppose that four times as much flow would be needed retrogradely to maintain cellular needs, or 80 to 120 mL/min. Although in many patients this does appear to be the case, our study uncovered many patients, particularly those with left ventricular hypertrophy, who required 250 to 300 mL/min to maintain homeostasis and to prevent myocardial ischemia.

Our study suggests that the degree of metabolic activity of some human hearts, unlike their experimental animal counterparts, may be quite high and must be met. This indicates that retrograde continuous warm cardioplegic protection of the myocardium is not guaranteed, but rather its effectiveness must be monitored. In this study, direct sampling of postcapillary blood gases appeared to be a simple and effective method of accomplishing this goal. Other simple methods, however, such as continuously monitoring myocardial PO_2 , usually cannot detect adequate myocardial delivery of substrate but merely detect the presence or absence of infused cardioplegia, in

the same way as the low-pressure alarm on the coronary sinus transducer in our study.

Last, our study demonstrates that myocardial energy needs can be met entirely by retrograde delivery of warm cardioplegia without the need for antegrade cardioplegia. As we [8] have previously shown with retrograde intermittent cold cardioplegia, antegrade cardioplegia imposes an unnecessary step and complicates an otherwise simple procedure. Moreover, it stretches the imagination a bit to believe that in a 2-hour cross-clamp period, a 2- to 3-minute dose of antegrade cardioplegia would have much influence on myocardial protection. Also, in redo operations, antegrade cardioplegia may impose dangers of its own in embolizing atheromatous debris from old vein grafts [13].

In conclusion, based on blood gas analysis of inflow and outflow cardioplegia samples in 100 patients, we have shown that retrograde continuous warm cardioplegia is capable of maintaining myocardial homeostasis and preventing myocardial ischemia in humans for up to 3 hours of aortic cross-clamping. Further, we have demonstrated variability in the metabolic needs of the warm, arrested human heart that sometimes seem at odds with and are greater in amount than experimental literature might suggest. During retrograde warm cardioplegia, the surgeon must ensure that the delivery of cardioplegia blood flow and volumes are sufficient to meet myocardial energy needs. In this study, this was easily achieved by sampling blood gases from arteriotomies. Finally, this study establishes that retrograde warm cardioplegia does not need an antecedent antegrade dose of cardioplegia to provide myocardial protection.

Much basic clinical research must be completed to understand the nature of retrograde delivery of cardioplegia to the capillary level and how to consistently measure the adequacy of this delivery. Although this study demonstrates the effectiveness of the technique of retrograde warm cardioplegia, it also imposes on the surgeon the necessity to monitor and confirm the adequacy of myocardial protection. At this stage in its development, we recommend continuous monitoring of coronary sinus

pressure, a standby low-pressure alarm, and intermittent sampling of coronary artery effluent for pH, P_{CO_2} , and PO_2 , with adjustment of retrograde flows accordingly.

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DISCUSSION

DR SIDNEY LEVITSKY (Boston, MA): I have a question that I think concerns many of us, and that is the problem of right heart versus left heart preservation during retrograde continuous warm blood cardioplegia. There is concern that much of the right heart coronary flow drains out through the thebesian veins, thus avoiding the coronary sinus. At New England Deaconess Hospital, we started using retrograde continuous warm blood cardioplegia in April 1991. Not infrequently, we have observed the absence of blood flow in the posterior descending coronary artery after arteriotomy in patients with a total occlusion of the right coronary artery. Nevertheless, these patients have a benign postoperative course with no evidence of right heart failure. Have you noticed any differences in oxygenation or pH, for example, between the right posterior descending or right marginal coronary vessels as opposed to the left-sided vessels?

DR GUNDRY: That is an excellent question and one that concerned us a great deal as we embarked on warm cardioplegia. We did notice a difference in samples taken from the right coronary artery or the posterior descending coronary artery in that they invariably had a lower pH and lower oxygen content. The oxygen tensions were often in the range of 10 to 15 mm Hg. However, when the data for the 100 patients were analyzed, none of these figures reached statistical significance compared with the other areas sampled in the heart. Using transesophageal echocardiography, we have looked at the function of almost all of these hearts, and much to our surprise, even with "lousy" right coronary artery blood gases, the right ventricular function of these hearts has been superb, better than I would have expected. But, yes, there seems to be a lower pH in those vessels and much more avid oxygen extraction. The flow is not as good to the right side.

DR GEORGE E. CIMOCHOWSKI (Wilkes-Barre, PA): That was an elegant presentation, Dr Gundry. My colleagues and I also have been interested in coronary effluents, and in the past 6 months, we have studied a small series of patients. We frequently turn off the retrograde flow for a short time, about 5 to 10 minutes, and did so in each of the study patients. We *never* turn it off in a patient with a hypertrophied ventricle.

We studied coronary effluents from the left anterior descending coronary artery. These were always measured after the last anastomosis, which in each case was the internal mammary artery. Initially we were timid; we stopped at 5 to 7 minutes and measured the pH and the PO_2 . The pH was quite good, 7.37. After we got a little more bold, we stopped it for 10 minutes, and our mean pH was 7.33, but there certainly was a range—7.11 to 7.52. We think that it is “probably” safe to stop retrograde flow for a short time. In our experience and probably in yours, the hypertrophied left ventricle with coronary artery disease is a flag.

I say that because there is a lot of variation in blood flow retrograde in the coronary sinus system. It is not simply a matter of giving cardioplegia in the coronary sinus and seeing it come out the coronary artery. An example is our recent case of an 85-year-old woman with coronary artery disease who was having a double-valve operation. During the mitral valve replacement, we noticed clinically there was good flow coming from the aorta. However, when we did the aortic valve replacement, we did not see good flow from the coronary ostia. We even gave antegrade cardioplegia and used a catheter with a manual inflating device. At 5 mL, we did not increase flow from the coronary ostia, and the patient died of low cardiac output. We subsequently took the heart to the autopsy suite, and at 6 mL in the balloon with the manual inflating device, there was free flow back and forth into the right atrium. With the self-inflating balloon, there was massive regurgitation.

Have you seen similar patients in whom the coronary sinus is so large that our equipment does not seem to cause the flow to go only retrograde?

DR GUNDRY: Yes, indeed. We have been impressed with the ability of the coronary sinus of a warm heart to expand. Unlike a cold heart, in which the coronary sinus and its surrounding fat tissue become quite rigid, during warm cardioplegia, the coronary sinus is really free to expand much like many other thin-walled veins. In fact, during valve replacement on several large hypertrophied hearts, we have used as much as 10 mL of air in an operator-inflated balloon to seal the coronary sinus. This is particularly important if you use transesophageal echocardiography, in that the anesthesiologist can put a Doppler probe across the coronary sinus proximal to the balloon. He or she can tell you how much air to inject into the balloon to seal the coronary sinus by looking at blood leaking around the balloon. It is often very dramatic.

Your point about hypertrophied hearts is extremely well taken. We have recently submitted an abstract to the Western Thoracic Surgical Association issuing a warning about hypertrophied hearts and some redo operations. This is a very dangerous area in retrograde continuous warm cardioplegia. We have got to be very careful and know a lot more about it before we can endorse it wholeheartedly.

DR CIMOCHOWSKI: We have done studies of the amount of blood flow coming out of the aorta retrogradely. As you raise the heart for the various maneuvers, by the time you get to the circumflex, you may have a 50% to 75% reduction in blood flow coming out the aorta. So all the answers are not in yet.

DR GUNDRY: That is correct. Even holding the heart to press on a circumflex area will dramatically change what comes out of that artery. Your assistant has to learn how to hold the heart in a slightly different way so as not to compress those veins.

DR PAUL T. FRANTZ (Roanoke, VA): I enjoyed your presentation very much. Based on our experience, the heart can tolerate intermittent ischemia during aerobic warm arrest. This experience involves 457 patients, 361 of whom had coronary bypass operations.

Our early technique was similar to that used in Toronto. In normothermic patients, we used intermittent antegrade and continuous retrograde cardioplegia while performing proximal and distal grafts with the aortic cross-clamp on.

Because of technical problems associated with retrograde catheters, we began using an intermittent antegrade technique. The appearance of multiorgan failure mentioned earlier led us to switch from normothermic to hypothermic systemic perfusion. One of our current techniques is to use intermittent antegrade cardioplegia, turning the solution off for 10 to sometimes 15 minutes. The proximal anastomosis is done after each distal graft. In some patients we use intermittent antegrade and intermittent retrograde cardioplegia, and in these situations, all the proximal grafts are done after the distal grafts have been completed.

There were 167 patients in whom we used the antegrade and retrograde technique. There were nine deaths and three myocardial infarctions in this group. Three patients required the balloon pump. The deaths were due to multiorgan failure (1), isolated ventricular fibrillation (2), preoperative myocardial infarction (1), sepsis (1), cerebrovascular accident (2), and hypertrophic cardiomyopathy (2). There was one preoperative massive myocardial infarction.

An intermittent antegrade technique was used in 194 patients. In this group there were only one death and three myocardial infarctions. Four patients required the balloon pump.

In our experience, the heart tolerates periods of interruption in cardioplegic flow. Based on your experience with the continuous retrograde technique, how do you explain this observation?

DR GUNDRY: I appreciate your comments and those of the last discussants about technique. As we are all practicing cardiac surgeons, we know that the heart can tolerate imperfection. We practice it nearly every day, unfortunately. We also know that a heart operated on 15 years ago, for example, that of a 45-year-old man undergoing placement of a couple of bypass grafts, could tolerate a cross-clamp across the aorta every 15 minutes, and the patient could come off bypass extremely easily. Unfortunately, I do not see those patients anymore; the cardiologists see them.

We are talking about applying a technique of preservation to a completely different stratum of patients, patients who cannot get a heart transplant because there are no donors; these patients have an ejection fraction of 0.15. As Dr Swain said a few minutes ago, it is one thing to take an ejection fraction of 0.60 and lose a third of it; the patient would leave the operating room smiling. When you take an ejection fraction of 0.20 and lose a third of it, the results include a left ventricular assist device, balloon pump, and death. So why tolerate any myocardial ischemia in a heart that if it loses three myocytes the patient may not leave the operating room alive? Hearts can tolerate ischemia; we prove that every day. However, we are trying to develop a technique where there is absolutely no ischemia. We are not quite there yet, but we are pretty close.

DR ROBERT A. GUYTON (Atlanta, GA): I have first a rebuttal to Dr Frantz. I think it is a dangerous and inappropriate leap of

faith to go from continuous warm cardioplegia to intermittent warm cardioplegia. I believe that is a backward step. There is abundant theoretical and experimental evidence that after 2 or 3 minutes of ischemia, myocardial damage begins. This is seen in nuclear magnetic resonance machines, in myocardial creatine kinase depletion, and in adenosine triphosphate depletion; repeated stunning of the heart causes metabolic damage. Because you can get away with something in the operating room does not mean that this is what is best for the heart in all situations, and I recommend that we not adopt intermittent warm cardioplegic techniques.

Second, Dr Gundry, I question and perhaps reject your hypothesis that sampling the coronary artery samples the heart because a hypoperfused region contributes very little to the sampled blood. If most of the blood is going to myocardium that is perfused, then that is what you are going to be sampling in the coronary artery. You do not sample the maybe 15% of the heart that is getting 2% of the cardioplegia because that 2% makes up such a small volume of what you are sampling. I think that to look at metabolism in a global way, you must sample globally and collect in a controlled situation the entire effluent.

DR GUNDRY: Thank you very much. I strongly echo your statements about the intermittent warm technique. As for sampling, what we tried to do was look at a regional sample as represented by a coronary artery and to compare that with the effluent from either a left coronary artery ostium or right coronary artery ostium. We could not find any difference between a regional area and a more global area. So I think an individual coronary artery sample can tell you what is happening in that region of interest at that point. A more global sample, such as that from a left main artery, can tell you more about what is happening to the heart as a whole.

Again, these are hypotheses. We hoped we proved or suggested we proved the hypothesis, but I take your point.

DR SAMUEL V. LICHTENSTEIN (Toronto, Ont, Canada): I congratulate you on an excellent study. It certainly puts some of our own concerns to rest. When Dr James Abel first introduced retrograde continuous warm blood cardioplegia in Toronto and the rest of us later adopted it, we were very concerned about the distribution of nutritive flow to the right ventricle and septum. The theory of warm heart surgery is based on the fact that electromechanical arrest reduces myocardial oxygen requirements to nearly minimal levels with little further benefit attributable to hyperthermia. You have referred to the warm arrested

heart as metabolically active. My question is, have you looked at retrograde continuous cold cardioplegia and compared its oxygen consumption with that of retrograde continuous warm cardioplegia?

DR GUNDRY: Anecdotally we have been able to do this in a very small number of patients. Because the cardioplegia is so cold, there is an extremely small drop in oxygen saturation or oxygen tension when studied across that capillary area. Whether that is because the heart is not metabolically active or much less metabolically active or because hemoglobin simply would not give up oxygen because of the cold, we cannot prove in a human model; we are trying to think of a way to do it.

Nevertheless, if you look at the basis of calculation and try to look at myocardial mass and oxygen consumption per mass, experimental studies suggest that myocardial metabolism of a warm, arrested heart drops to about 10% of that of the normal working heart. If you calculate even a 25% capillary crossing of retrograde flow, that is a nutrient blood flow of 25%; in most hearts the calculations work out well; about 125 to 150 mL of flow should meet metabolic demands. But in about half of the hearts, we had to go to higher flows, contradicting what calculations from animals tell us should have been adequate to meet the heart's demands. These flows are with the balloons inflated. So there is a lot we do not know.

DR CONSTANTINE E. ANAGNOSTOPOULOS (New York, NY): My colleagues and I abandoned the use of isolated experimental retrograde perfusion some years ago because we observed myocardial edema. I have not heard about any methods you use at present to assess whether you have myocardial edema with a higher flow, for example, echocardiography. Furthermore, I understand that you have tried to use your samples as regional samples, but perhaps if you used pulmonary artery vents and tied the superior and inferior venae cavae, you would be able to have better representation of a global specimen.

DR GUNDRY: Your points and contributions are well taken. We have looked at intermittent retrograde cardioplegia and low-flow retrograde cardioplegia in an experimental model in edema, and like the Emory group, we could find no increase in myocardial edema. Apparently, based on their report earlier today, they also could not confirm myocardial edema with their continuous high-flow retrograde method. It does not seem to be a clinical concern.

Optimal Pleurodesis: A Comparison Study

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With the resurgence of thoracoscopy, there is renewed interest in less invasive methods of pleurodesis. We wished to compare in an animal model a variety of methods suggested in reports. The purpose of the study was to rank the effectiveness of each procedure against the standard mechanical pleurodesis. Twenty-five mongrel dogs (weight, 25 to 35 kg) underwent bilateral thoracotomy. Each animal was randomly assigned to receive two of the following methods of pleurodesis: tetracycline, talc, mechanical abrasion, neodymium:yttrium-aluminum garnet (Nd:YAG) laser (Hereus Inc, E. Rutherford, NJ) photocoagulation, and argon beam coagulator (ABC) (Beacon Lab, Bloomfield, CO) electrocoagulation of the parietal pleura. At evaluation at 30 ± 2

days, the efficacy of pleurodesis was graded on a scale of 0 to 4, with 0 representing a complete absence of pleural symphysis and 4 the adhesion of more than one lobe to both the chest wall and mediastinum. Mean grade and standard deviation of each method were: talc, 3.0 ± 0.67 ; mechanical, 3.0 ± 0.82 ; tetracycline, 2.3 ± 1.4 ; ABC, 1.5 ± 0.97 ; and Nd:YAG laser, 0.7 ± 0.95 . Both the talc and mechanical methods were superior to either the Nd:YAG laser or the ABC ($p < 0.01$). In this study, neither the Nd:YAG laser nor the ABC proved efficacious in producing pleurodesis. Talc poudrage is the only method of pleural symphysis comparable with mechanical abrasion.

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Pleurodesis is commonly performed for recurrent or persistent pneumothoraces or chronic pleural effusion. The current definitive treatment includes thoracotomy, bleb resection, and mechanical pleural abrasion or pleurectomy. Although effective, open pleurodesis subjects the patient to the morbidity of thoracotomy, which includes general anesthesia, postoperative atelectasis, pneumonia, and the unknown long-term functional effects of dividing large muscle groups. Furthermore, patients with chronic pleural effusion often are at high risk for a major operation owing to preexisting malignancy or cardiopulmonary disease. Recently, the resurgence of thoracoscopy has led to a renewed interest in less invasive methods of pleurodesis. Reported alternatives have included talc poudrage [1, 2], instillation of various chemical sclerosing agents [3, 4], and thoroscopically guided pleural scarification with either the neodymium:yttrium-aluminum garnet (Nd:YAG) laser [5] or the argon beam coagulator.

To date, the majority of studies on methods of pleurodesis have been limited to clinical trials in which the efficacy of pleurodesis was determined by the rate of recurrence of pneumothorax or pleural effusion. In this study, we wished to conduct a controlled comparison study of reported methods of pleurodesis by using an

animal model. The efficacy of pleurodesis for each method was then "ranked" against the standard open pleurodesis and mechanical abrasion.

Material and Methods

All animals were housed and procedures performed in the facilities of Northwestern University Medical School, Chicago, IL. Animals received humane care in accordance with the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH publication No. 85-23, revised 1985).

Twenty-five mongrel dogs (weight, 25 to 35 kg) underwent bilateral standard thoracotomy through the fifth intercostal space. Because thoracoscopic visualization of the entire pleural surface in the dog is difficult, thoracotomies were performed to ensure visual confirmation of adequacy of the surgical pleurodesis. The canine model was used because of the durability of the animal to withstand bilateral thoracotomies and a cavity size large enough so that all instrumentation could be used with equal facility on all parts of the pleura. Anesthesia was induced with acepromazine (0.1 mg/kg) and sodium thiamylal (4% solution, 0.5 mL/kg) and maintained with halothane.

Each animal was randomly assigned to receive two of the following methods of pleurodesis: (1) mechanical dry gauze abrasion, (2) chemical sclerosis with 500 mg of tetracycline hydrochloride, (3) talc poudrage (1 g asbestos-free talc), (4) Nd:YAG laser photocoagulation, and (5) argon beam electrocoagulation of the parietal pleura. This

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totalled 10 hemithoraces per experimental group. The randomization code allowed some animals to receive the same method bilaterally. Mechanical abrasion was performed by rubbing gauze against the pleural surface until punctate hemorrhages were produced but the integrity was not disrupted. Tetracycline (0.016 g/kg) was diluted in 100 mL of saline solution and sprayed on the pleural surface. The residual fluid was not evacuated from the chest. This is a similar dose to that used clinically (0.014 g/kg diluted in 250 mL of saline solution). Talc was applied in a similar manner. A suspension of 1 g was mixed in 100 mL of saline solution and sprayed in the chest. Neodymium:yttrium-aluminum garnet laser pleurodesis was performed with a 1064-nm laser from Heu-reus Inc, E. Rutherford, NJ, set at 50 W continuous wave in a focused mode through a hand probe (2-mm spot size). Photocoagulation of the pleura overlying all accessible ribs was performed until there was gross carboniza-tion of the parietal pleura. This was done to simulate clinical situations. Mean energy applied per pleurodesis was 7,800 J. Argon beam electrocoagulation used an argon beam coagulator (Beacon Lab, Bloomfield, CO) coupled to a standard electrocautery unit. A flexible delivery catheter allowed access to the pleura overlying all visible rib surfaces. An energy setting of 35 W was used and the pleura coagulated until a black char was produced. Oper-ative time for each side averaged 1.5 hours.

In all procedures, the chest was closed over a thoracos-tomy tube, which was removed under positive-pressure ventilation at the conclusion of the operation. Lung ex-pansion (which was complete in all cases) was confirmed by postoperative roentgenogram. Buprenorphine hydro-chloride was administered every 12 hours for 48 hours for postoperative analgesia.

All animals were allowed to recover and then observed for a mean of 30 ± 2 days. After the animals were killed, a median sternotomy was performed and the efficacy of pleurodesis graded on a scale of 0 to 4:

- 0 = Complete absence of adhesions
- 1 = Periincisional adhesions only
- 2 = Adhesion of one lobe to chest wall or mediastinum
- 3 = Adhesion of more than one lobe to chest wall or mediastinum
- 4 = Adhesion of more than one lobe to chest wall and mediastinum

The use of codes at autopsy assured that the investigators were blinded as to the type of pleurodesis each animal had received.

Data were expressed as mean $\pm$ standard deviation of the mean. The paired Student's *t* test was used to deter-mine the differences between each group. A *p* value of less than 0.05 was considered statistically significant.

Results

A total of 50 pleurodesis procedures were performed on 25 animals. One animal that received Nd:YAG laser pleurodesis died on postoperative day 4. Autopsy re-

Table 1. Results of Pleurodesis

Technique	Grade ^a
Mechanical abrasion	3.0 ± 0.82
Talc poudrage	3.0 ± 0.67
Tetracycline	2.3 ± 1.4
Argon beam coagulator	1.5 ± 0.97^b
Nd:YAG laser	0.7 ± 0.95^b

^a Values are shown as mean $\pm$ standard deviation. ^b *p* < 0.01 versus talc poudrage and mechanical abrasion.

Nd:YAG = neodymium:yttrium-aluminum garnet.

vealed a massive hemothorax and a focal area of necrosis in the intercostal muscle overlying a neurovascular bun-dle. This animal was replaced. All other animals survived the procedure and recovered without complication. Ani-mals were killed at a mean of 30 ± 2 days after operation. The mean grade and standard deviation for each grade are shown in Table 1.

Talc poudrage and mechanical abrasion were equally effective in producing pleural symphysis. Both methods were significantly superior to either the Nd:YAG laser or the argon beam coagulator group (*p* < 0.01). Chemical sclerosis with tetracycline was consistently more effective in producing pleural symphysis than either laser tech-nique; however, the difference was not statistically signif-icant.

Qualitatively, the adhesions produced by talc poudrage and mechanical abrasion were more dense, requiring sharp dissection for their lysis, than those produced by the other three methods.

Comment

Spontaneous pneumothorax is one of the most common of the diseases faced by a thoracic surgeon. Typically, it occurs without warning in young, healthy males and is caused by a subpleural bleb at the lung apex. Ipsilateral recurrences are common, and the risk of recurrence in-creases with each episode, ranging from 20% after the initial episode to up to 80% after a third pneumothorax [6, 7]. Treatment with a thoracostomy tube alone results in reexpansion of the lung and some minimal degree of pleural symphysis due to pleural abrasion by the tube itself. Although this approach is effective in the majority of patients, 20% to 30% will have recurrence warranting more aggressive attempts at pleurodesis. Thoracotomy with bleb resection and mechanical abrasion is the most effective treatment but is a major surgical procedure associated with serious morbidity. Less invasive methods include the instillation of various sclerosing agents, talc poudrage, and, most recently, laser scarification of the parietal pleura. Previous studies on methods of pleuro-desis have been limited to clinical trials, which have found recurrence rates of 13% to 25% for tetracycline sclerosis [1, 8, 9], 3% to 8% for talc poudrage [1, 2], and 7% for Nd:YAG laser pleurodesis [5].

In this study we were able to assess the ability of five

different methods of pleurodesis under controlled conditions in an animal model. The dog is a large animal, which allows easy access to all of the pleural surface with current clinical instrumentation. Also, because the dog does not form adhesions well, we considered it a severe test that would give the greatest difference between techniques. Rats and rabbits have been used in some adhesion experiments because they form adhesions easily. We were concerned that all methods might produce dense adhesions and thus not afford an opportunity to distinguish among the methods.

Because this study was designed to apply directly to patients, each method was applied in a similar manner to the clinical situation. It is difficult if not impossible to control all variables in surgical techniques, so we used them as we have in humans. The surgical principles, power settings, and methods of application approximated as closely as feasible our operative technique. With the exception of Nd:YAG laser scarification, our results compare favorably with the clinical trials cited above. Talc poudrage was the only method comparable with standard mechanical abrasion in this canine model. Clinically, no sclerosing agent has been found to have a lower recurrence rate than that reported for talc.

"Closed" methods of pleurodesis fail, in part, because they do not address the underlying lung pathology, ie, pulmonary blebs. Recently, interest in thoracoscopic bleb ablation has been fueled by studies documenting the CO₂ laser's ability to seal pulmonary air leaks [10] and by clinical trials employing electrocautery [11] and laser energy [12] to coagulate pulmonary blebs. Rusch and associates [13], using a rabbit model, found the argon beam coagulator to be as effective as electrocautery in sealing pulmonary air leaks and to cause less acute tissue injury than standard electrocautery. Theoretically, any method that can successfully seal or ablate pulmonary blebs should decrease the risk of recurrent pneumothorax.

Chronic pleural effusions represent the other most common indication for pleurodesis. These patients are often elderly and have severe cardiopulmonary disease or malignant effusions secondary to end-stage cancer. Life expectancy in this group of patients is limited and recurrence of pleural effusion inevitable after simple drainage. Therefore, pleurodesis must be accomplished in the simplest, least invasive manner. Recent studies have compared sclerosis with bleomycin and tetracycline [14] as well as talc poudrage [15] for treatment of malignant effusions. As with spontaneous pneumothoraces, talc poudrage was found to be superior in preventing recurrence of malignant pleural effusion.

In this study, talc poudrage was the most efficacious closed method of pleurodesis and comparable with mechanical abrasion. Concern over the long-term safety of talc poudrage has been unfounded. Long-term follow-up studies by Lange and associates [16], Viskum and co-workers [17], and the British Thoracic Association [18] have found only a mild restrictive impairment of lung function and no increased risk of mesothelioma or lung cancer 20 to 40 years after talc poudrage for spontaneous or recurrent pneumothoraces. The incidence of recurrent

pneumothorax after talc poudrage in these studies was 2% to 3%.

In summary, we advocate simple thoracostomy tube drainage for the initial episode of spontaneous pneumothorax. The 20% to 30% of patients who have recurrence should undergo thoracoscopy with attempted bleb ablation and pleurodesis. As thoracoscopic techniques become more familiar and improve, the procedure should be able to be done under local anesthesia. Finally, patients with chronic pleural effusions would best be served by thoracoscopy and talc poudrage to limit the number of procedures in a debilitated patient with an often limited life expectancy.

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DISCUSSION

DR RODNEY J. LANDRENEAU (Pittsburgh, PA): I want to thank Drs Bresticker and LoCicero for allowing me to discuss this report. I first would like to comment that I firmly agree with them that the most important thing in the management of the spontaneous pneumothorax is to control the underlying pulmonary pathology. I have a bit of a problem, however, with the use of talc as the means of providing pleural symphysis in situations of benign disease. I would refer to a recent article by Drs Curtis Tribble and Tom Daniel from the University of Virginia, appearing in *The Annals of Thoracic Surgery*, where they recently recommended talc poudrage for variety of clinical conditions. However, I have learned from recent discussions with Dr Daniel that he now refrains from using talc poudrage for most benign pleural disease. Talc is a very effective means of managing the malignant effusion, or malignant process, but for primary or spontaneous pneumothorax I think that this is not an appropriate application because of the intense pleuritic reaction it can cause. I furthermore agree that laser or argon beam coagulation is a relatively ineffective way of primarily handling these problems.

I have two questions for Dr Bresticker. Do you have in mind a subsequent study comparing chemical pleurodesis with bleomycin or other alternative antibiotic sclerosants, such as doxycycline, with talc as a control? Second, the advent of thoroscopic video-assisted thoracic surgery basically allows the same operation, a stapled resection of apical bullous disease and mechanical pleurodesis through the thoroscopic ports, to be accomplished with minimal operative morbidity. With the advent of this new procedure, are you still of the opinion that talc poudrage is the most effective way of handling the problem of spontaneous pneumothorax?

DR BRESTICKER: In response to the first question, we chose tetracycline primarily because it has traditionally been the most widely used. We do hope to in future studies compare bleomycin and doxycycline, which is what we use now that tetracycline is no longer available. We did not use bleomycin in this study for two reasons: because of its expense and because we did not know the systemic effects of intrapleural bleomycin in the canine model.

And it is true, in response to your second question, that as equipment and the techniques of thoracoscopy improve, mechanical abrasion could be performed through the thoracoscope, and this would supplant talc poudrage as the preferred method of pleurodesis.

DR HERMES C. GRILLO (Boston, MA): Just one word of caution. Many years ago I had very successful results with talc pleurodesis through a thoracoscope in one hospital. I later performed the same procedure in another hospital and had a high incidence of recurrence. Grabowski and Malt [1] illuminated this some years ago when they studied talc as a generic material and found it varied in composition from different sources with great variability in the power to instigate adhesions. Some talcum powder is benign whereas some other produces firm adhesions.

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Intrapleural Quinacrine Instillation for Recurrent Pneumothorax or Persistent Air Leak

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From 1982 to 1990, 27 patients with recurrent pneumothorax or persistent air leak (28 episodes) underwent pleurodesis with intrapleural administration of quinacrine, according to a standardized scheme. A first evaluation was done about 1 month after the intervention. In August 1990, all patients were invited for a second check-up. In 4 patients quinacrine plasma concentrations were determined. There was one early failure. No late recurrences were observed. Neither serious nor late complications were seen with our low-dose regimen. Tran-

sient fever was the only constant side effect. In contrast to other chemicals proposed for pleurodesis, quinacrine did not cause major pain. Only very low quinacrine plasma concentrations (peak, <10 ng/mL) were found. In conclusion, chemical pleurodesis with quinacrine can be considered a safe and effective treatment. The number of administrations as well as the dosage are important to prevent morbidity and recurrence.

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It is claimed that patients with recurrent pneumothorax or persistent air leak should undergo a surgical intervention [1] and that, if operation should be avoided, tetracycline pleurodesis remains the alternative of choice [2]. However, intrapleural administration of tetracycline can be very painful, and surgical pleurodesis demands general anesthesia and is not without morbidity. Moreover, the production of injectable tetracycline hydrochloride for pleurodesis has been recently discontinued [3].

In 1982, we first introduced quinacrine pleurodesis at our institution as a treatment of recurrent pneumothorax or persistent air leak in patients who were in poor general condition and hence were bad candidates for surgical pleurectomy. Our initial results were very satisfactory and prompted us to use this technique for patients with pneumothorax who were referred for operation. The present retrospective study was performed because quinacrine pleurodesis is still not a widely accepted treatment for pneumothorax.

Material and Methods

From September 9, 1982, until August 25, 1990, 27 patients with persistent air leak (air leak persisting beyond 4 days despite adequate tube drainage) or recurrent pneumothorax were treated, after informed consent, with chemical pleurodesis by intrapleural administration of quinacrine hydrochloride. All patients had previously been treated by chest tube drainage.

Quinacrine hydrochloride, 100 mg dissolved in 50 mL of sterile physiological saline solution (prepared in our hospital pharmacy), was injected through the thorax

drain, which was then closed for 1 hour. Active suction (-20 cm H_2O) was then restarted. If the magnitude of the air leak did not allow the drain to be clamped, the drain was suspended as described by Almassi and Haasler [4]. Quinacrine was given once daily on 4 consecutive days. The drain was clamped 24 hours after the last injection. About 48 hours after the last injection, chest radiography was performed; if lung expansion had been maintained the drain was removed. Doses were chosen in accordance with the report of Larrieu and associates [5].

An ambulant check, including radiography of the chest, was performed about a month after therapy. Moreover, in August 1990, all patients, with the exception of patient 11 (the early failure), were invited for anamnestic, clinical, and radiological check-up. Only 24 of the remaining 26 patients could be reevaluated, because 2 patients died of causes not related to the pleurodesis; those patients, however, did not have recurrence.

In 4 patients quinacrine plasma concentrations were measured by high-performance liquid chromatography and fluorescence detection, as described by Björkman and Elisson [6].

Results

Twenty-eight episodes of pneumothorax in 27 patients were treated with quinacrine pleurodesis. Table 1 shows the patient characteristics. Seventeen patients had eighteen episodes of spontaneous pneumothorax. Among them, 6 had radiographic signs of severe emphysema and 1 (with bilateral pneumothorax) had cystic fibrosis. Quinacrine pleurodesis was performed in these patients because of a recurrence of pneumothorax in 11 and because of a persistent air leak in 7. One patient suffered pneumothorax with a persistent air leak after blunt chest

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Table 1. Patient Characteristics

Patient No.	Age (y)	Sex	Side	Cause of Pneumothorax or Air Leak	Previous Pneumothoraces	Previous Treatment
1	28	M	Right	Lobectomy	0	Drain 10 d
2	67	M	Left	COLD	1	Drain 28 d
3	47	F	Right	Blunt trauma	0	Drain 14 d
4	27	M	Right	Spontaneous	0	Drain 8 d
5	75	M	Left	COLD, ventilated	0	Drain 14 d + tetracycline
6	59	M	Right	COLD	2	Drain 6 d
7	31	M	Right	Spontaneous	0	Drain 4 d
8	53	M	Left	Pleural puncture	0	Drain 27 d
9	46	M	Right	Lobectomy	0	Drain 11 d
10	73	M	Left	COLD	2	Drain 20 d + tetracycline
11	56	M	Right	COLD	1	Drain 21 d + tetracycline
12	24	M	Right	Spontaneous	0	Drain 11 d
13	45	F	Right	Spontaneous	0	Drain 5 d
14	29	M	Right	Spontaneous	1	Drain 7 d
15	51	M	Right	Spontaneous	1	Drain 23 d + tetracycline
16a	13	M	Right	Cystic fibrosis	1	Drain 8 d
16b	13	M	Left	Cystic fibrosis	1	Drain 8 d
17	43	F	Right	Spontaneous	0	Drain 14 d + tetracycline
18	61	M	Left	Lobectomy	0	Drain 11 d
19	20	M	Right	Subclavian vein puncture	0	Drain 10 d
20	18	M	Left	Spontaneous	4	Drain 15 d
21	17	M	Left	Spontaneous	3	Drain 2 d
22	15	F	Left	Spine operation	0	Drain 10 d
23	50	M	Right	Segmentectomy	0	Drain 10 d
24	19	M	Right	Bilobectomy	0	Drain 11 d
25	29	M	Right	Bilobectomy	0	Drain 10 d
26	61	M	Right	COLD	0	Drain 10 d
27	21	M	Left	Spontaneous	2	Drain 10 d + tetracycline

COLD = chronic obstructive lung disease; F = female; M = male; tetracycline = attempt at tetracycline pleurodesis without success.

trauma. Nine patients had to be treated because of a persistent air leak of operative or iatrogenic origin: 6 among them after lobectomy, bilobectomy, or segmentectomy, 1 after a spine operation, 1 after pleurocentesis, and 1 after subclavian vein puncture.

Thorax drainage had been instituted for a mean of 12 days, and 6 patients had previously been treated (in another hospital) without success with at least one attempt of tetracycline pleurodesis 7 to 15 days before quinacrine pleurodesis. All patients received the four planned quinacrine administrations. One patient, patient 18, needed six quinacrine injections for complete healing.

Episodes of major pain were not reported, and analgesics were not administered during or after the quinacrine injection. Fever developed in all but 3 patients but always disappeared within 48 hours after the last injection.

Patient 5 was in intensive care and on a ventilator because of a severe pneumonia superimposed on a chronic obstructive lung disease. While he was being ventilated an important (>8 L/min) and persistent (thorax drainage for 14 days and failure of tetracycline pleurodesis) air leak developed. He was successfully treated with quinacrine pleurodesis while still being ventilated.

Patient 11 had generalized emphysema and was treated in another hospital for right-sided pneumothorax. He underwent 3 weeks of drainage and one tetracycline pleurodesis. After removal of the drain, recurrence occurred and the patient was referred to our department. A new thoracostomy was performed, showing an air leak of about 2 L/min. The lung expanded and four quinacrine applications were given. The patient was discharged without problems but had to be hospitalized again 13 days later for a second recurrence. Thoracotomy was performed and basal fibrinous adhesions were found. The apical pneumothorax was treated with a pleurectomy. The patient did not tolerate the thoracotomy and died 13 days after the operation of respiratory failure.

Late recurrences, defined as a recurrence occurring after 1 month, were not observed over a mean follow-up period of 30.5 months (standard deviation, 29.0 months; range, 0.5 month to 89.0 months).

Quinacrine plasma concentrations were measured in 4 patients. In 2 of them, plasma concentrations were not detectable (<0.2 ng/mL). In the other 2 patients a very rapid uptake of quinacrine from the pleural space, with a peak concentration within 30 minutes, was seen. How-

ever, only very low quinacrine plasma concentrations were found (peak concentrations, 7.8 and 3.7 ng/mL; concentrations after 2 hours, 0.8 and 0.5 ng/mL).

Minimal air-fluid levels shown by radiography after pleurodesis in 3 patients disappeared spontaneously after 4 weeks.

Comment

Many substances have been used to obtain chemical pleurodesis: kaolin, silver nitrate, talc, cyanoacrylate, dicetylphosphate, olive oil, blood, camphor oil, tetracycline, 50% dextrose solution, and quinacrine [7, 8]. More recently, thoracoscopic application of fibrin glue has been proposed, with varying short-term and long-term recurrence rates (4.4% to 25%) [9-11].

Quinacrine hydrochloride, a semisynthetic alkaloid, was the first low-toxicity antimalarial [12]. It has been used for treatment of malignant pleural, pericardial, and peritoneal effusions [13]. The use of quinacrine for pneumothorax patients is recommended by Boat [14], Cattaneo [15], Kattwinkel [16], Jones [17], and their associates. Larrieu and colleagues [5] in 1978 published the first study comparing quinacrine pleurodesis with surgical pleurectomy (20 patients in the quinacrine pleurodesis group).

The present study confirms that intrapleural administration of quinacrine is a very effective treatment for complicated pneumothorax. There was only one treatment failure: 27 of 28 cases were successfully treated and among these cases, no recurrences occurred.

Intrapleural administration of quinacrine appears to be well tolerated by patients. Moderate to high fever was observed in most patients, probably caused by pleural inflammation rather than by systemic reactions. Indeed, serum levels of quinacrine in 4 patients remained undetectable or very low.

Although the present series is relatively small, the recurrence rate after quinacrine pleurodesis (1/28) tends to approximate the low recurrence rates of a surgical procedure.

It was beyond the scope of the current study to examine how these satisfactory results were obtained. In contrast to pleurodesis with tetracyclines or talc, quinacrine was repeatedly administered. It is very likely that these results do not only depend on the product itself, but also on the repeated administration of the drug. The observation in patient 18 that a residual pneumothorax after four quinacrine applications disappeared after two extra administrations further supports this contention.

Tetracycline and talc pleurodesis remain very painful even when adequate doses of sedation and analgesics are given [18]. The finding that the pain associated with quinacrine pleurodesis is of a much lesser degree represents a considerable advantage. Moreover, quinacrine was successful in 5 of the 6 patients with recurrence after tetracycline pleurodesis.

Several side effects of quinacrine used in a higher dose (400 mg daily or more) have been reported: fever, pain,

nausea, vomitus, ileus, hallucinations, hypotension, dyspnea, yellow skin pigmentation, headache, and convulsions [19, 20]. However, with the exception of fever and minor pain we did not see any of these early side effects. It has been suggested that the frequency and severity of complications are dose related [21]. To our knowledge, late complications never have been mentioned.

In conclusion, this study suggests that pleurodesis with repeated low doses of quinacrine represents a successful and almost painless treatment of recurrent pneumothorax or persistent air leak. Prospective trials with more patients should be designed to further evaluate this potential advantage and reassess the recurrence rate after quinacrine pleurodesis in spontaneous and idiopathic pneumothorax.

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INVITED COMMENTARY

This article is a useful reaffirmation of the effectiveness of this method of treatment of recurrent pneumothorax or pleural effusion and persistent air leak. Initially, a relatively high dose (greater than 500 mg) of intrapleural quinacrine hydrochloride was used in patients considered to be at high risk for open operation, and toxicity was substantial. However, after considerable experience with a lower dose regimen (100 mg of quinacrine intrapleurally daily for 4 days) we recommended this as the initial treatment of choice for patients with recurrent spontaneous pneumothorax. As with Janzing and associates, our patients usually experienced fever, 70% versus greater than 80% in the present report. Thirty percent of our patients did require mild analgesics versus essentially none of Janzing and associates' patients, but discomfort is modest at worst, far less than with even a limited thoracotomy and certainly less than with talc or tetracycline pleurodesis. We also had a low success rate with intrapleural instillation of tetracycline and with 50% glucose, and tetracycline for intrapleural use is no longer available in the United States. Although sterile vials of parenteral quinacrine hydrochloride are also no longer commercially available, instructions for preparation by hospital pharmacies are included in our referenced 1979 article.

To summarize the reported experience with the four daily dose regimen, quinacrine pleurodesis is effective in 95% of cases. On actuarial analysis, it is as effective on early and late (4 years) follow-up as scarification or pleurectomy, yet is associated with significantly fewer complications than operation (5% versus approximately 40%) and a 30% shorter average length of stay. Although average length of stay with tube thoracostomy alone is an additional 30% shorter, a recurrence rate of more than 20% within 1 year confirms the ineffectiveness of this approach in cases of recurrent pneumothorax.

A concern is that quinacrine pleurodesis may be too good. How formidable will the worst-case adhesions be in

a patient with cystic fibrosis subsequently coming to transplantation? In a report of postmortem findings after this treatment, discussed in our article, both pleural spaces were completely adhered. Of the 21 patients with pneumothoraces who we treated between 1971 and 1977, 1 patient suffered a small ipsilateral recurrence 2 years after quinacrine instillation. Although this patient did come to operation at another institution, relatively dense adhesions were encountered, indicating that operation was almost certainly not needed. Further, the patient required reoperation for bleeding. Can a treatment be too effective? Although Janzing and associates have in 1 case extended the number of instillations required in a resistant case to six (a measure of the low toxicity and discomfort associated with the method) possibly the majority of patients only need two or three instillations localized at the apex. A prospective clinical or laboratory trial of various doses and positions versus operation could be of considerable interest.

In the meantime, I support Janzing and associates' recommendation that intrapleural instillation of quinacrine for treatment of recurrent spontaneous pneumothorax appears to be the treatment of choice. With worldwide increasing concerns about patients' safety and medical care costs, this treatment is less invasive even than the thoracoscopic approaches described more recently and is less expensive in both the short and long term than any other approach.

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Secondary Spontaneous Pneumothorax

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To assess the clinical manifestations and therapy of secondary spontaneous pneumothorax (SSP), 123 episodes of SSP in 67 patients were retrospectively reviewed and were compared with 254 episodes of primary spontaneous pneumothorax in 130 patients. The major underlying lung diseases associated with SSP were emphysema (22 patients) and tuberculosis (21 patients). The average age of patients with SSP was 66.8 years, and the most common symptom was dyspnea. The average arterial oxygen tension at onset of SSP was 61.1 ± 12.1 mm Hg (mean $\pm$ standard deviation), which was lower than that of patients with primary spontaneous

pneumothorax ($p < 0.01$). The recurrence rate of open thoracotomy with pleural abrasion was 12.5% (3 of 24 episodes), which was not lower than that of thoracostomy tube drainage with chemical pleurodesis using tetracycline (recurrence rate, 18.8%) ($p > 0.5$). We concluded that considering the high age of the patients, the presence of underlying lung diseases, and the increased operative risk, thoracostomy tube drainage rather than open thoracotomy was preferred as the first choice of therapy for SSP.

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Spontaneous pneumothorax is classified into primary and secondary spontaneous pneumothorax. Primary spontaneous pneumothorax (PSP) occurs in healthy individuals without a coexisting lung disease, usually as a result of rupture of a pulmonary bleb. Secondary spontaneous pneumothorax (SSP) is a pneumothorax that is related to the presence of an underlying lung disease such as chronic obstructive lung disease or pulmonary tuberculosis [1]. The clinical manifestations and treatment of PSP are well-documented and established, and there is minimal morbidity and no mortality when properly treated. However, in SSP, which often occurs in older individuals, the morbidity and mortality rates may be substantial, regardless of adequate therapy [2]. The purpose of this report is to describe the clinical manifestation of SSP and also to assess the management, especially by open thoracotomy, of SSP.

Material and Methods

A total of 197 patients with 377 separate episodes of spontaneous pneumothorax treated at National Gifu Hospital from January 1, 1984, to December 31, 1988, were reviewed for this study. Pneumothoraces secondary to trauma or iatrogenic causes were excluded. Among these episodes of spontaneous pneumothorax, 123 episodes (32.5%) in 67 patients (34.0%) were related to the presence of obvious coexisting lung diseases and were categorized as SSP.

All medical records of patients with spontaneous pneumothorax were reviewed, and those of patients with SSP were compared with those of patients with PSP. Follow-up was accomplished by review of outpatient records

or by telephone interview, and the minimum length of follow-up was 2 years. The average length of follow-up in SSP was 4.1 years, and that in PSP was 4.3 years. Counts were compared with the use of χ^2 analysis. Continuous data were compared by Student's *t* test if they were approximately normally distributed, or by a Mann-Whitney U test if not.

Results

Underlying Diseases

The most common underlying disease was pulmonary emphysema, and 45 episodes (36.6%) in 22 patients (32.8%) occurred with this disease (Table 1). Twenty-eight episodes (22.8%) in 21 patients (31.3%) occurred with pulmonary tuberculosis. Pneumoconiosis was a cause of 26 episodes (21.1%) of spontaneous pneumothorax in 9 patients (13.4%). Less commonly, pneumothoraces occurred secondary to pulmonary fibrosis (9 episodes in 5 patients), primary lung cancer (4 episodes in 4 patients), sarcoidosis (2 episodes in 2 patients), or bronchial asthma (4 episodes in 2 patients). Pneumonia, diffuse panbronchiolitis, and eosinophilic granuloma were a cause of pneumothorax in 1 patient each.

Sex and Age

Sixty-one patients with SSP were male, and 6 were female (Table 2). The average age at the diagnosis of SSP was 66.8 years (range, 12 to 85 years), and was significantly greater than that of patients with PSP ($p < 0.01$).

Clinical Manifestations

The most common symptom of SSP was dyspnea, which occurred in 79 episodes (64.2%), whereas patients complained of dyspnea in only 26 episodes of PSP (10.2%) ($p < 0.01$) (see Table 2). Chest pain, the most common

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Table 1. Underlying Diseases Associated With Secondary Spontaneous Pneumothorax

Disease	No. of Patients (female)	No. of Episodes
Emphysema	22 (0)	45
Tuberculosis	21 (3)	28
Pneumoconiosis	9 (0)	26
Pulmonary fibrosis	5 (2)	9
Primary lung cancer	4 (1)	4
Sarcoidosis	2 (0)	2
Asthma	2 (0)	4
Pneumonia	1 (0)	1
Diffuse panbronchiolitis	1 (0)	1
Eosinophilic granuloma	1 (0)	3
Total	67 (6)	123

symptom in PSP, was complained of in only 49 episodes of SSP (39.8%). Four patients with SSP were asymptomatic, with diagnosis made on a routine roentgenogram, whereas only 1 patient with PSP was asymptomatic, but the difference was not statistically significant ($0.05 < p < 0.1$).

Arterial oxygen tension at the onset of SSP was 61.1 ± 12.2 mm Hg (mean $\pm$ standard deviation), which was significantly less than the arterial oxygen tension at onset of PSP ($p < 0.01$). Arterial oxygen tension after resolution of SSP was 76.5 ± 13.0 mm Hg, which was also less than the arterial oxygen tension after resolution of PSP ($p < 0.01$).

Nonoperative Therapy

Ninety-nine of 123 episodes of SSP (80.5%) were treated with nonoperative procedures, whereas 154 of 254 episodes of PSP (60.6%) were treated with nonoperative procedures (Table 3). This difference is statistically significant ($p < 0.01$). Nonoperative procedures included bed-

Table 2. Clinical Findings in Patients With Spontaneous Pneumothorax^a

Variable	SSP	PSP	p Value
No. of Patients	67	130	
Sex (M/F)	61/6	116/14	NS
Age (y)	65.2 ± 14.7	26.8 ± 11.0	<0.01
No. of episodes	123	254	
Chief complaints at onset			
Dyspnea	79	26	<0.01
Chest pain	49	216	<0.01
Cough	14	36	NS
Asymptomatic	4	1	NS
PaO ₂ (mm Hg)			
At onset	61.1 ± 12.2	81.2 ± 11.5	<0.01
After resolution	76.5 ± 13.0	94.6 ± 6.7	<0.01

^a Values are shown as the mean $\pm$ the standard deviation where indicated.

NS = not significant; PaO₂ = oxygen tension; PSP = primary spontaneous pneumothorax; SSP = secondary spontaneous pneumothorax.

Table 3. Treatment of Spontaneous Pneumothorax

Variable	SSP	PSP	p Value
Nonoperative therapy	99 (80.5%)	154 (60.6%)	<0.01
Observation	10 (8.1%)	59 (23.2%)	<0.01
Needle aspiration	11 (8.9%)	12 (4.7%)	NS
Tube drainage	78 (63.4%)	83 (32.7%)	<0.01
Without pleurodesis	46	81	
With pleurodesis ^a	32	2	
Open thoracotomy	24 (19.5%)	100 (39.4%)	<0.01
Indications for open thoracotomy			
Recurrent episodes	4	58	<0.01
Persistent air leak	13	22	<0.01
Large blebs or bullae	6	18	NS
Bilateral pneumothorax	1	2	NS

^a Pleurodesis was performed using tetracycline.

NS = not significant; PSP = primary spontaneous pneumothorax; SSP = secondary spontaneous pneumothorax.

rest and observation in 10 episodes, needle aspiration in 11 episodes, and thoracostomy tube drainage in 78 episodes. In 32 of 78 episodes treated with tube drainage, chemical pleurodesis using tetracycline was performed.

Operation and Indications

Only 24 episodes of SSP (19.5%) were treated with open thoracotomy, whereas 100 episodes of PSP (39.5%) were treated with open thoracotomy ($p < 0.01$) (see Table 3). The most common indication for open thoracotomy of SSP was a persistent air leak, which accounted for 15 of 24 episodes of SSP (62.5%), whereas only 22 of 100 episodes of PSP (22.0%) were treated with open thoracotomy due to a persistent air leak ($p < 0.01$). The other indications in SSP were recurrent episodes (4 episodes), large blebs or bullae (4 episodes), and bilateral pneumothorax (1 episode). On the other hand, the most common indication of open thoracotomy for PSP was recurrent episodes (58 of 100 episodes).

A transaxillary approach was used in open thoracotomy for both SSP and PSP. Total excision of blebs and bullae and oversewing of the area were performed in 22 patients with SSP and in all 100 patients with PSP. Right pneumonectomy of the destroyed lung was performed in 1 patient and right upper lobectomy was performed in the other patient with SSP. Pleural abrasion with a dry gauze was also performed in all but 1 patient with SSP. Parietal pleurectomy was not performed in any of the patients with SSP. Pleural abrasion was performed in all patients with PSP.

Recurrence

Recurrence occurred in 38 of 123 episodes of SSP (30.9%) (Table 4). The recurrence rate with open thoracotomy was 12.5%, which was less than that with nonoperative therapy (35.4%) ($0.02 < p < 0.05$). The recurrence rate with thoracotomy tube drainage with chemical pleurodesis was only 18.8%, which was comparable with that with open thoracotomy ($p > 0.5$).

Table 4. Recurrence Rates of Various Treatments in Patients With Secondary and Primary Spontaneous Pneumothorax

Treatment	SSP	PSP	p Value
Nonoperative therapy	35.4% (35/99) ^a	44.8% (69/154)	NS
Observation	20.0% (2/10)	52.5% (31/59)	<0.05
Needle aspiration	45.5% (5/11) ^a	58.3% (7/12)	NS
Tube drainage	35.9% (28/78) ^a	37.3% (31/83)	NS
Without pleurodesis	47.8% (22/46) ^a	38.2% (31/81)	NS
With pleurodesis	18.8% (6/32) ^b	0.0% (0/2)	NS
Open thoracotomy	12.5% (3/24)	3.0% (3/100)	<0.01
Total	30.9% (38/123)	28.3% (72/254)	NS

^a Significance: $p < 0.05$, nonoperative therapy versus open thoracotomy in secondary spontaneous pneumothorax. ^b Significance: $p < 0.05$, tube drainage with pleurodesis versus without pleurodesis in secondary spontaneous pneumothorax.

NS = not significant; PSP = primary spontaneous pneumothorax; SSP = secondary spontaneous pneumothorax.

The overall recurrence rate in patients with PSP was 28.3% (72 of 254 episodes), which was comparable with that in patients with SSP (30.9%). Only 3 of 100 patients with PSP (3.0%) treated with open thoracotomy had a recurrence, whereas 3 of 24 patients with SSP (12.5%) treated with open thoracotomy had a recurrence ($0.02 < p < 0.05$).

Eleven of 38 recurrences in SSP (28.9%) occurred within 1 month or less, 16 recurrences (42.1%) in 1 to 6 months, one recurrence (2.6%) in 6 to 12 months, and four recurrences in 1 to 2 years (Fig 1). Thus, 32 recurrences in SSP (84.2%) occurred within 2 years of the previous episode. The average time to recurrence in SSP was 280.0 ± 77 days ($\pm$ standard error), which was similar to that in PSP (338.1 ± 55.7 days).

Complications

There were no complications related to nonoperative therapy for both SSP and PSP. No intraoperative complications occurred. There were 9 postoperative complications in SSP: 7 air leaks that persisted more than 5 days, 1

pneumonia, and 1 heart failure (Table 5). The average postoperative chest tube placement interval in SSP was 4.3 ± 2.3 days ($\pm$ standard error), which was significantly longer than that in PSP ($p < 0.01$).

Mortality

Twelve patients with SSP died (Table 6), whereas no patients with PSP died. One patient (patient 7) who had open thoracotomy and in whom an air leak persisted postoperatively died of pneumonia 10 days after operation. Six patients (patients 1, 2, 3, 4, 5, and 6) died before the pneumothorax had resolved. All of these 6 patients died within 1 month after the onset of the pneumothorax. Five patients (patients 8, 9, 10, 11, and 12) died after pneumothorax had resolved; 4 of these patients died within 2 months after the pneumothorax had resolved. Patient 12 with pulmonary tuberculosis died 9 months after the pneumothorax had resolved, due to development of lung cancer.

Comment

Spontaneous pneumothorax commonly occurs in young male patients without any apparent lung disease; it occurs less commonly in patients with underlying lung disease, which is categorized as secondary [1, 3]. The most common underlying lung disease in our series was, as has

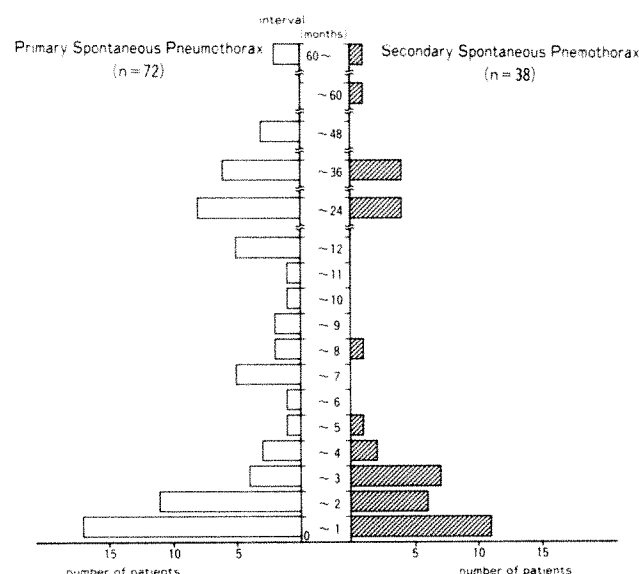


Fig 1. Interval between resolution of pneumothorax and recurrence.

Table 5. Postoperative Complications

Complications	SSP	PSP	p Value
Prolonged air leak (more than 5 days)	7	3	<0.01
Days that air leak persisted after operation ^a	4.3 ± 2.3	1.5 ± 1.2	<0.01
Pneumonia	1	0	NS
Heart failure	1	0	NS
Hemothorax	0	1	NS
Respiratory failure	1	0	NS

^a Mean $\pm$ the standard deviation.

NS = not significant; PSP = primary spontaneous pneumothorax; SSP = secondary spontaneous pneumothorax.

Table 6. Fatalities With Secondary Spontaneous Pneumothorax

Patient No.	Age (y)	Sex	Underlying Disease	Cause of Death	Interval Between Pneumothorax Onset and Death
Patients who died before pneumothorax was resolved					
1	62	Male	Lung cancer	Lung cancer	7 days
2	68	Male	Lung cancer	Radiation pneumonitis	2 days
3	83	Male	Tuberculosis	Tuberculosis	9 days
4	64	Male	Tuberculosis	Pneumonia	10 days
5	84	Male	Pneumonia	Pneumonia	10 days
6	48	Male	Pulmonary fibrosis	Respiratory failure	21 days
7	71	Male	Emphysema	Operation-related death	20 days
Patients who died after pneumothorax was resolved					
8	70	Male	Emphysema	Pneumonia	7 days
9	70	Female	Lung cancer	Lung cancer	2 years
10	58	Male	Tuberculosis	Tuberculosis	50 days
11	84	Male	Emphysema	Pneumonia	21 days
12	81	Male	Tuberculosis	Lung cancer	9 months

already been reported [1, 2], pulmonary emphysema, accounting for 36.6% of cases of SSP. Pulmonary tuberculosis accounted for 22.8% in our series, whereas Getz and Beasley [4] reported that only 3 (10.7%) of 28 secondary pneumothoraces were related to pulmonary tuberculosis [4]. This may suggest that in our country, Japan, the prevalence of tuberculosis remains high.

The most common symptom in patients with SSP was not chest pain, which was the most common symptom in patients with PSP, but was dyspnea; in patients with SSP, who are usually older than those with PSP and also have previously diminished lung function because of underlying lung diseases, even a small pneumothorax can produce severe respiratory distress [5].

Management and Recurrence

Spontaneous pneumothorax may be treated with observation, needle aspiration, thoracostomy tube drainage with or without pleurodesis, or open thoracotomy. The choice of therapy must be based on the severity and duration of symptoms, the presence of an underlying pulmonary disease, a history of previous episodes, and the occupation of the patient. In management of our patients with SSP, tube drainage was performed in 78 episodes (63.4%), and observation and needle aspiration were performed in only 10 episodes (8.1%) and 11 episodes (8.9%), respectively. Shields and Oilschlager [2] reported that observation was carried out in only 7 episodes (11.7%), needle aspiration in only 4 episodes (6.7%), and thoracostomy tube drainage in 39 episodes (65.0%) in a series of 49 men 40 years of age and older with 60 episodes of spontaneous pneumothorax. Patients with SSP should be treated with tube drainage regardless of the size of pneumothorax for rapid reexpansion of functioning lung tissue, whereas bed-rest or needle aspiration has been reevaluated in selected healthy young patients with a small pneumothorax [1, 2, 5]. In these patients, air leaks sometimes last more than 10 days, but because of a significantly increased operative risk, tube

drainage should be continued for a longer period than in PSP.

The risk of recurrent pneumothorax varies widely in published reports because of the varying age and associated lung disease patterns of the patients. DeVries and Wolfe [6] estimated that there was a 32% recurrence rate among patients treated with nonoperative methods. Granke and co-workers [7] reported that 11 of 49 patients treated with tube drainage had a recurrence (22.4%), and there were no recurrences in the operative group of 78 patients. Seremetis [8] reported a 49% rate (21 of 44) of recurrence in patients treated with bed-rest, a 38% recurrence rate (31 of 81) in those treated with tube drainage, and no recurrence after open thoracotomy. Schoenenberger and co-workers [9] reported that recurrence rates were 30% after 10 ± 10 months in both PSP and SSP. Thus, the recurrence rates observed in our series of 30.9% in SSP and 28.3% in PSP are comparable with figures seen in other series.

To prevent recurrence, the diseased site should be resected and the pleural space obliterated. Pleural space obliteration is accomplished by chemical pleurodesis, mechanical pleural abrasion, or partial pleurectomy. Chemical pleurodesis is a blind procedure and can result in adhesions that are too dense and in scars over some pleural areas, with inadequate adhesions in other areas; this can result in serious pleural complications. In spite of these disadvantages, chemical pleurodesis finds occasional application in the prevention of recurrence in patients with serious respiratory impairment due to underlying lung disease in whom thoracotomy for pleurectomy or pleural abrasion would carry an unacceptable risk. Thoracostomy tube drainage with chemical pleurodesis using tetracycline was used in 32 of our episodes of SSP. The recurrence rate was 18.8%, which is significantly less than that of observation alone, needle aspiration, or tube thoracotomy without pleurodesis, and was comparable with that of open thoracotomy with pleural abrasion. Many surgeons continue to consider bleb resection

and dry gauze pleural abrasion, which was employed in our series, to be effective in preventing recurrence [10]. Youmans and co-workers [11] reported their clinical experience with pleural abrasion (only one recurrence in 30 patients). But our result (recurrence rate with pleural abrasion, 12.5%) suggests that pleural abrasion is not adequate to prevent recurrence in SSP.

Weeden and Smith [12] reported their results of pleurectomy and demonstrated only a 3.7% major complication rate (8/241). The recurrence rate was only 0.43% (one in 233 patients) [12], which may be lower than the recurrence rate (12.5%) in our series treated with pleural abrasion. Deslauriers and co-workers [13] reported that only 2 (0.6%) of 409 patients treated with pleurectomy had a recurrence. Moreover, Weeden and Smith [12] reported no significant change in the results of respiratory function tests performed before and 6 months or more after pleurectomy. Thus, they advocated the use of transaxillary apical pleurectomy for the younger age group, and a full pleurectomy in the older age group, who often have chronic obstructive lung disease that is not confined to the apex of the upper lobe.

Morbidity and Mortality

Even though most patients with SSP can be managed successfully, death may result from respiratory failure caused by the pneumothorax, particularly in older patients with extensive underlying lung disease. Shields and Oilschlager [2] reported a 16.3% mortality rate (8 of 48 patients) in patients more than 40 years old. Six of these eight deaths were contributed to or were directly the result of the pneumothorax. Dines and co-workers [14] reported 10 of 57 patients with SSP associated with emphysema who died as a result of spontaneous pneumothorax, and concluded that although an uncommon complication, spontaneous pneumothorax is most serious and requires emergency thoracostomy tube drainage.

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Continuous Intercostal Nerve Block Versus Epidural Morphine for Postthoracotomy Analgesia

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Twenty patients undergoing elective thoracotomy were randomized into two groups, receiving either lumbar epidural morphine (n = 10) or continuous extrapleural intercostal nerve block (n = 10). Subjective pain relief was assessed on a linear visual analogue scale. Pulmonary function (peak expiratory flow rate, forced expiratory volume in 1 second, and forced vital capacity) was measured on the day before operation and daily for 4 days after operation. Pulse oximetry monitoring was used to determine the incidence of hypoxemia. No significant difference was observed between the groups concerning pain relief (except at 28 hours, in favor of the

intercostal nerve block group), respiratory performance, or arterial oxygen saturation. Vomiting, pruritus, and urinary retention occurred only in the epidural group, whereas nausea occurred significantly less frequently in the extrapleural group. We conclude that after thoracotomy continuous extrapleural intercostal nerve block is as effective as lumbar epidural morphine in reducing postoperative pain and restoring pulmonary mechanics. Because of the significantly lower complication rates we favor continuous extrapleural intercostal nerve block for postthoracotomy analgesia.

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Thoracotomy causes severe postoperative pain and marked impairment of pulmonary functions [1]. Conventional analgesia using opiates has been shown to be inadequate [2] and may contribute to further deterioration of pulmonary mechanics by impairing the natural sigh mechanism [3]. Epidural analgesia using local anesthetic agents provides effective postthoracotomy analgesia but is associated with a high incidence of complications including hypotension from bilateral sympathetic blockade [4]. Epidural opiates are widely used to provide postthoracotomy pain relief [5, 6] but may be associated with a high incidence of complications including nausea and vomiting, urinary retention, pruritus, and delayed respiratory depression, which is unpredictable and insidious in onset [7].

We have previously shown that continuous extrapleural intercostal nerve block provided effective analgesia after thoracotomy and aided postoperative recovery of pulmonary functions [8, 9]. Its use for up to 5 days has not been associated with any significant complications. We believe that continuous extrapleural intercostal nerve block may provide as good an analgesia as epidural analgesia without the associated complications. This study was designed to prove this by comparing lumbar epidural morphine with continuous extrapleural intercos-

tal nerve block with bupivacaine after elective thoracotomy.

Patients and Methods

Patient Selection

This study was approved by the hospital's ethics committee. Written informed consent was obtained from 20 adults undergoing elective thoracotomy for pulmonary and esophageal procedures. Exclusion criteria included marked obesity, known sensitivity to morphine or bupivacaine, substantial preoperative analgesic consumption, and standard contraindications to epidural catheter insertion.

Perioperative Period

Patients were given preoperative instructions on the use of a hand-held spirometer (Respiradyne; Chesbrough-Pond's Ltd, Greenwich, UK) and the linear visual analogue scale consisting of a 10-cm graduated line with 0 indicating no pain and 10 indicating the worst pain imaginable. Patients were premedicated with temazepam. Upon arrival in the anesthetic room patients were randomized to receive either epidural morphine (group A) or extrapleural bupivacaine (group B).

Before the induction of anesthesia patients in group A had an epidural catheter inserted into the lumbar epidural space at the L2-3 interspace. The epidural placement of the catheter and the lack of spinal block were confirmed by a 4-mL test dose of 1% plain lignocaine. General

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Table 1. Starting Doses of Epidural Morphine^a

Patient Age (y)	Dose (mg)
15-44	6
45-65	5
66-75	4
76+	2

^a Undiluted 0.1% preservative-free morphine is used.

anesthesia was induced with thiopentone, and a competitive muscle relaxant was used to aid tracheal intubation with a double-lumen endobronchial tube. Anesthesia was maintained with 50% nitrous oxide in oxygen and a delivered concentration of 0.5% to 2% isoflurane. Intraoperative systemic opiates were avoided in both groups.

Patients in group B received general anesthesia as described. Before closure of the chest, the parietal pleura overlying the paravertebral space was lifted. The paravertebral space was then entered using Lahey forceps. The catheter was inserted via a 16-gauge disposable Touhy (Portex Ltd, Hythe, UK) needle. The tip of the catheter was inserted into the paravertebral space for a distance of 3 to 4 cm. The parietal pleura was then loosely reattached, as previously described [8].

Approximately 60 minutes before the end of the operation patients in group A received a bolus of morphine in preservative-free normal saline solution epidurally (Table 1), and patients in group B received a bolus of 20 mL of 0.5% bupivacaine through the extrapleural catheter before the end of the operation.

All patients were extubated at the end of the operation. In the recovery room both groups were given oxygen at 4 L/min by face mask. This was continued for 24 hours. No further oxygen was given unless oxygen saturations fell below 90%. Group A received an infusion of 50 µg/mL morphine in normal saline solution through the epidural catheter at a rate of 100 µg/h, based on previously described technique [9]. Group B patients had an infusion of bupivacaine at a dose of 0.5 mg · kg⁻¹ · h⁻¹ with a concentration of 5 mg/mL through the extrapleural catheter. In addition, patients had access to intramuscular omnopon and rectal diclofenac as requested. No attempt was made to withhold requested analgesia. Personnel taking measurements and personnel setting up the infusion were kept "blind."

Monitoring

Postoperative monitoring was carried out as recommended by Ready and associates [5] and consisted of hourly respiratory rates and sedation levels for 24 hours, dropping to every 4 hours thereafter. Temperature, pulse rate, and blood pressures were measured every 4 hours.

Postoperative pain was assessed by the patients themselves on the visual analogue scale. Pain scores were recorded at 4-hour intervals for a total of 4 days. Nausea, vomiting, pruritus, urinary retention, and the use of additional analgesics were recorded. Twenty-four-hour continuous pulse oximetry was also recorded.

Respiratory function tests (peak expiratory flow rate, forced expiratory volume in 1 second, and forced vital capacity) were performed preoperatively and daily postoperatively in the sitting position using a Respiradyne after 5 mg of nebulized salbutamol. The best of three measurements was recorded. Results were expressed as a percentage of preoperative values.

Statistics

The results were analyzed using the Kruskal-Wallis one-way analysis of variance by ranks and the Mann-Whitney U test to determine statistical significance.

Results

The groups were comparable with respect to age, smoking habits, body habitus, and surgical procedures (Table 2).

Pain Relief

Both techniques provided good analgesia as demonstrated by low pain scores. There was no significant difference between the groups, except at 28 hours when continuous extrapleural intercostal nerve block provided significantly better analgesia. No significant difference was observed in the use of rectal diclofenac (6 patients in group A, 8 in group B). One patient in each group required one opiate supplementation, whereas 3 patients in group B required opiate injection twice.

Postoperative Pulmonary Function

The mean values of peak expiratory flow rate, forced expiratory volume in 1 second, and forced vital capacity as a percentage of preoperative control values were maximally reduced at 24 hours in both groups. There was no statistically significant difference between the two groups.

Pulse Oximetry

There was no significant difference in the arterial oxygen saturation between the two groups.

Complications

Table 3 shows the complications associated with each method of analgesia. There were significantly ($p < 0.05$) higher incidences of vomiting requiring antiemetic treatment, pruritus, and urinary retention requiring urinary

Table 2. Characteristics of Patients

Characteristic	Group A	Group B
Mean (range) age (y)	57.4 (24-67)	59 (35-79)
Sex (M:F)	5:5	8:2
Diagnoses		
Lung malignancy	8	7
Benign lung tumor		1
Antireflux procedure	2	2
Left/right thoracotomy	9/1	6/4
Mean (range) body weight (kg)	68.4 (55-110)	67.0 (55-89)

Table 3. Incidence of Complications

Complication	Group A	Group B	<i>p</i> (binomial)
Nausea	6	2	
Vomiting	3	...	<0.05
Pruritus	4	...	<0.05
Urinary retention	4	...	<0.05
Respiratory depression ^a	...	...	
Confusion	...	1	

^a Defined as a respiratory rate less than 8 breaths per minute.

catheterization in the epidural group. More patients who received epidural morphine complained of nausea than those in the extrapleural group, but this was not statistically significant. No periods of excessive somnolence or a respiratory rate of less than 8 per minute were detected in any patient. One elderly patient in group B had an episode of confusion that responded to a 6-hour cessation of infusion.

Comment

The unilateral nature of most thoracic surgical procedures makes intercostal nerve blocks feasible. We have recently demonstrated that the site of action of continuous extrapleural intercostal nerve block is in the paravertebral space [10]. The paravertebral space is the ideal site not only because the intercostal nerves are in small bundles without fascial sheath but also because local anesthetic agents here effectively block the posterior primary rami and the ipsilateral sympathetic chain [11]. Blocking the posterior primary rami after thoracotomy relieves backache caused by straining of vertebral muscles and ligaments of the costovertebral and costotransverse ligaments. Unilateral sympathetic block may have a useful effect on the endocrine-metabolic response to operation without the hypotension associated with bilateral sympathetic block from epidural block [12]. We previously demonstrated in a randomized, double-blind control study that continuous extrapleural intercostal nerve block using bupivacaine is efficacious in producing postthoracotomy analgesia and in aiding postoperative recovery of pulmonary mechanics, thus preventing postoperative pulmonary complications [8]. Measurements of bupivacaine levels have not demonstrated toxic levels being achieved (Berrisford RG, Sabanathan S, Mearns AJ; unpublished results), and bupivacaine toxicity did not develop in any patient after 5 days of infusion.

After thoracotomy, epidural opiate is effective whether infused by the lumbar or the thoracic routes [13]. There is evidence that the quality of analgesia from opiates is no different whatever routes they are given [14]. Centrally administered opiates are effective in smaller doses. The rostral spread of opiates, however, may result in delayed respiratory depression, which may be unpredictable. This has been described in up to 13.5% of patients [7], although large-scale studies have quoted rates of 0.25% to 0.9% [15, 16]. We did not detect any patients with this complication in this series. The high incidence of the other

complications of epidural morphine, including urinary retention, nausea, vomiting, and pruritus, have been previously observed [15]. These potential complications, which may be life-threatening in the case of delayed respiratory depression, mean that diligent observations and intensive nursing care are mandatory.

The placement of the paravertebral catheter at thoracotomy can be achieved under direct vision expeditiously. With experience, epidural catheterization can be performed without much delay, although failure of cannula insertion has been described in up to 10.9% of patients [17]. With minimal modification in technique, the paravertebral block can also be effectively applied after parietal pleurectomy [18].

We have demonstrated in this study that continuous extrapleural intercostal nerve block provided as good an analgesia as epidural morphine and has similar beneficial effects on postoperative pulmonary functions. The lack of complications with continuous intercostal nerve block, with an understanding of its mechanism of action, means that this method is a safe and effective analgesia after thoracotomy. We believe it should be more widely used in view of its simplicity and safety.

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INVITED COMMENTARY

In this study Richardson and associates compare treatment of postthoracotomy pain by continuous infusion of morphine into the lumbar epidural space versus their previously described technique of infusing local anesthetic into the extrapleural paravertebral space. The extrapleural technique is somewhat similar to the method of intrapleural anesthetic administration that has recently enjoyed popularity. Theoretically, the extrapleural technique may offer advantages over intrapleural administration of local anesthetics. Because the local anesthetic is deposited closer to the intercostal nerves, without needing to diffuse across the parietal pleura, the analgesic efficacy may be greater. In addition, analgesia is probably less dependent on patient positioning, and the chest tubes do not need to be clamped to prevent the local anesthetic from being removed.

Although Richardson and associates found comparable analgesia with fewer side effects using their extrapleural technique, the reader needs to be aware that the epidural morphine regimen used for comparison may not be the optimal implementation of that technique. They relied on relatively low doses of epidural morphine administered in a small volume (2 mL/h) through a lumbar catheter far removed from the level of the thoracotomy. Although lumbar epidural opioid administration can be used effectively to treat postthoracotomy pain, larger doses or volumes of solution are necessary as compared with administration in the thoracic region. Indeed, the study

Richardson and associates cite as the basis for their epidural opioid technique [9] used thoracic catheters and doses of morphine 3 to 6 times greater than those used in the current study.

The reader should also be aware that the bupivacaine infusion used for extrapleural analgesia represents more than twice the maximum recommended dose for a 24-hour period (400 mg). Although Richardson and associates state that they did not see any complications or side effects in their extrapleural group, it seems likely to us that the confusion experienced by one of their patients may have been due to bupivacaine toxicity. This is supported by their statement that the confusion resolved by stopping the infusion for 6 hours.

In summary, we applaud Richardson and associates for developing an effective alternative method for providing postthoracotomy analgesia. However, we believe that the safety and superiority of their method over existing techniques still needs to be confirmed in a larger series of patients.

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Continuous Intercostal Analgesia With 0.5% Bupivacaine After Thoracotomy: A Randomized Study

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This study was undertaken to evaluate the effectiveness of 0.5% bupivacaine (360 mg/day) as a continuous infusion through an indwelling intercostal catheter inserted intraoperatively in the management of pain after thoracotomy. Eighty-six patients were randomized into three groups: group 1 = intercostal bupivacaine, group 2 = intercostal saline solution, and group 3 = fixed-schedule intramuscular buprenorphine. Supplementary buprenorphine was given as required. Pain and pulmonary function were assessed throughout the first 5 days after operation. Pain score was lower in group 1 than in group 2 for the first 8 hours after operation ($p < 0.02$). During the first 3 postoperative days, mean postoperative pain

scores of 5 or more were recorded in 9% of group 1 patients versus 40% of group 2 patients ($p < 0.05$) and 13% of group 3 patients (not significant). Total doses of buprenorphine were lower in groups 1 and 2 than in group 3 ($p < 0.001$). No between-group differences in pulmonary function were observed. Respiratory complications occurred in no patients in groups 1 and 3 versus 5 in group 2 ($p < 0.05$). Continuous intercostal bupivacaine provided similar early pain control as compared with fixed-schedule narcotics but induced better analgesia with fewer complications than on-demand narcotics alone (group 2).

(*Ann Thorac Surg* 1993;55:381-5)

Narcotics are effective in controlling postoperative pain but are associated with respiratory depression and suppression of the cough reflex. This has led to a persistent search for methods of pain relief that do not contribute per se to depressed pulmonary function. Intercostal nerve blockade using intermittent injections of 0.5% bupivacaine hydrochloride has been proved effective in providing pain relief after abdominal and thoracic operations [1, 2]. Continuous intercostal analgesia with an infusion of 0.5% bupivacaine hydrochloride through an indwelling catheter placed extrapleurally during thoracotomy has therefore been proposed [3] as a means for maintaining analgesia over a prolonged period after thoracotomy. In an attempt to evaluate the effectiveness of continuous intercostal analgesia with 0.5% bupivacaine without epinephrine as compared with fixed-schedule or on-demand intramuscular narcotics, we conducted the following randomized, prospective study in 86 patients after thoracotomy.

Material and Methods

After obtaining the approval of the Paris-Sud University Human Investigation Committee as well as written informed consent from our patients, 86 patients (61 men and 24 women) undergoing lobectomy or wedge resection

through a posterolateral thoracotomy in the fifth intercostal space were studied from September 1989 to January 1991. Patients with abnormal preoperative pulmonary function tests or a history of allergy to local anesthetics were excluded.

The patients were randomized into three experimental groups: group 1 = continuous intercostal 0.5% bupivacaine hydrochloride without epinephrine ($n = 26$), group 2 = continuous intercostal 0.9% saline solution ($n = 26$), and group 3 = intramuscular buprenorphine sulfate, 0.3 mg three times daily ($n = 34$).

Technique

Before closure of the thoracotomy, a multiperforated epidural catheter (Perifix; Laboratoires Bruneau, Paris, France) was inserted percutaneously through a 16-gauge needle into the chest cavity through the anterior part of the fifth intercostal space. The needle was removed, and after slight peeling of the parietal pleura, the tip of the catheter was introduced into the extrapleural space and advanced under direct visual guidance from the neck of the fifth rib to the neck of the second rib. The catheter was positioned 3 to 4 cm from the spine. The parietal pleura was then stitched and the catheter was firmly secured to the skin. To ensure that there was no intrapleural leakage, 10 mL of 0.9% saline solution was injected through the catheter. Two chest tubes were placed anteriorly and posteriorly, and the chest was closed. These chest tubes were connected to water sealed drainage with 20 cm H₂O suction and were removed on the fifth postoperative day.

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Identically appearing vials of 20 mL of 5% bupivacaine chlorhydrate or 20 mL of 0.9% saline solution were supplied by the Laboratoire Roger Bellon, Neuilly sur Seine, France. Each patient was allocated to one trial solution, identified by a number. At the conclusion of the operative procedure, 20 mL of the assigned solution was injected into the extrapleural space through the catheter. The intercostal catheter was connected through a bacterial Millipore filter to an infusion pump, and 3 mL/h of the solution was continuously infused for the first 5 postoperative days. The catheter was removed on the fifth postoperative day.

Study Protocol

The daily dose of bupivacaine (group 1) was 360 mg. In group 3 patients, 0.3 mg of intramuscular buprenorphine sulfate was given every 8 hours for the first 5 postoperative days. In each experimental group, the standard dose of rescue on-demand narcotic (intramuscular buprenorphine sulfate, 0.3 mg) was administered whenever any of the patients complained of pain.

During the study period, the patients assessed pain severity every 4 hours using the visual pain analog scale of El-Baz and associates [4] (0 = no pain; 10 = most severe pain imaginable). This visual pain analog scale shows five facial expressions for different degrees of pain positioned near the appropriate score on the scale.

Pulmonary function tests were performed by the physical therapist with the patient seated on the day before operation and on days 1, 3, 5, and 10 after operation; vital capacity and forced expiratory volume in 1 second were measured with a dry spirometer (Autospiro AS-600; Minato Medical Science Co, Osaka, Japan). Maximal static inspiratory and expiratory pressures at the mouth were measured according to the method of Black and Hyatt [5].

Heart rate, systolic and diastolic blood pressures, and temperature were monitored throughout the study. A chest roentgenogram was taken every day. Any complications and unusual events were recorded.

Analysis

The three therapeutic regimens to be compared were intercostal blockade with bupivacaine and on-demand narcotics (group 1), intercostal saline solution (placebo) and on-demand narcotics (group 2), and fixed-schedule narcotics and on-demand narcotics (group 3). Analysis of variance and χ^2 analysis were used to compare the three groups with regard to age, height, weight, sex, diagnosis, preoperative pulmonary function, length of procedure, and type of lung resection (wedge resection or lobectomy). For pain scores analysis, scores were averaged for each day and analyses were performed for the following blocks of time: first 8 hours postoperatively, first, second, third, and fourth postoperative days, and morning of the fifth postoperative day. To look for significant differences among treatment groups or over time in pain scores and pulmonary function tests, a multivariate analysis of variance with the Sheffé procedure for multiple comparisons was used. To compare percentages of patients with severe pain (mean pain score of 5 or more from postoperative

Table 1. Patient Characteristics^a

Variable	Group 1 (bupivacaine)	Group 2 (saline solution)	Group 3 (buprenorphine)
No. of Patients	26	26	34
Age (y)	56 ± 3	53 ± 3	56 ± 2
Weight (kg)	66 ± 2	65 ± 2	72 ± 2
Duration of operation (min)	166 ± 9	140 ± 9	168 ± 6
Operation performed			
Single lobectomy (%)	85	90	88
Wedge resection (%)	15	10	12

^a Where applicable, values are shown as mean ± standard error of the mean.

day 0 to 3) in the three groups, χ^2 analysis was used. Side effects and complications in the three groups were compared by χ^2 analysis. Analysis of variance was used to compare treatment groups with respect to supplemental narcotic use. A *p* value less than 0.05 was regarded as the threshold for statistical significance. Results are given as mean ± standard error of the mean.

Results

The patients in the three groups were similar with regard to age, weight, height, sex, diagnosis, duration of operation, and pulmonary function tests (Table 1).

Among the 86 patients, 76 completed the study. Three patients in group 1 and 3 patients in group 2 were excluded (malposition of the catheter in 3 patients and plugging of the lumen in 3 patients). Five patients in group 3 were excluded because they did not complete the visual pain analog scale during the entire study period.

Figure 1 shows the mean pain scores measured using the pain score analog scale. As compared with group 2 (placebo), pain scores were lower in group 1 (bupivacaine) in the first 2 postoperative days, and the difference was significant for the first 8 hours postoperatively (5.2 ± 0.4 versus 3.6 ± 0.4 , respectively; $p < 0.02$). During the first 3 postoperative days (Fig 2), only 9% of the patients in group 1 (bupivacaine) had a mean postoperative pain score of 5 or more as compared with 40% in group 2 (placebo) ($p < 0.05$) and 13% in group 3 (buprenorphine) (not significant). Similar amounts of supplemental buprenorphine were given in groups 1 and 3. However, the mean total dose of buprenorphine given throughout the 5 study days was significantly lower in groups 1 (1.95 ± 0.03 mg) and 2 (1.85 ± 0.03 mg) than in group 3 (4.8 ± 0.04 mg; $p < 0.001$).

All patients had severe reductions in vital capacity, forced expiratory volume in 1 second, and maximal inspiratory and expiratory pressures on day 1 with incomplete recovery on day 10 (Fig 3). There were no significant differences between the groups at any time in the absolute values of vital capacity, forced expiratory volume in 1 second, or maximal inspiratory and expiratory pressures

or in decreases in these parameters as compared with preoperative values. There were no correlations at any time between pain scores and any parameter of pulmonary function. There were no differences in heart rate, systolic and diastolic blood pressure, or temperature between the three groups throughout the study.

No complications developed related to the intercostal catheter or to administration of intercostal bupivacaine. Five respiratory complications (21%) occurred in group 2 (saline solution) (atelectasis in 3 patients, pneumopathy in 2 patients), as compared with none in group 1 (bupivacaine) ($p < 0.05$) and group 3 (buprenorphine) ($p < 0.05$).

Comment

This prospective, randomized study was designed to determine whether continuous intercostal infusion of 0.5% bupivacaine could provide good postoperative pain relief as compared with fixed-schedule or on-demand narcotics.

Analysis of self-assessed pain scores in our patients provided support for this hypothesis. In terms of postoperative pain relief, intercostal bupivacaine blockade was superior to on-demand intramuscular narcotics (group 2; saline solution) but similar to fixed-schedule intramuscular narcotics. However, the total amount of narcotics used was lower with intercostal bupivacaine than with fixed-schedule intramuscular narcotics.

The daily dose of bupivacaine given was 360 mg, which is approximately half the daily dose used by others for intermittent or continuous administration of intercostal bupivacaine [6-9]. With this dosage no evidence of bupivacaine toxicity was observed in our patients. However,

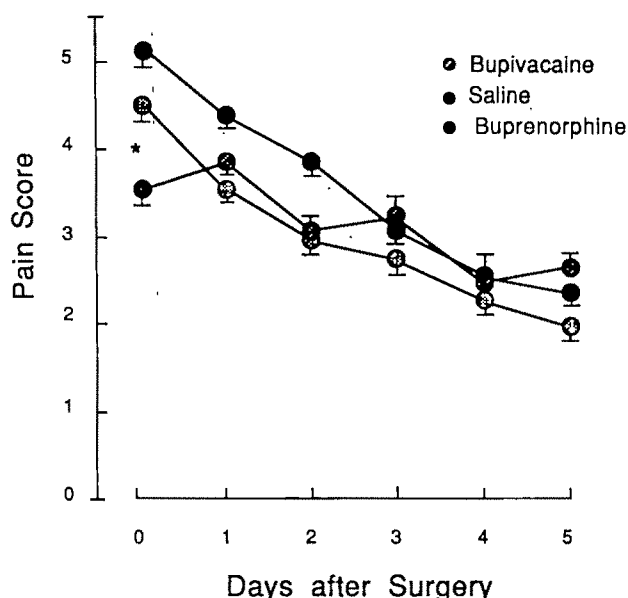


Fig 1. Each point represents an averaged self-assessed pain score and standard error of the mean for a given observation period in each of the three experimental groups. (Day 0 = first 8 hours after operation; * $p < 0.02$, intercostal bupivacaine compared with intercostal saline solution.)

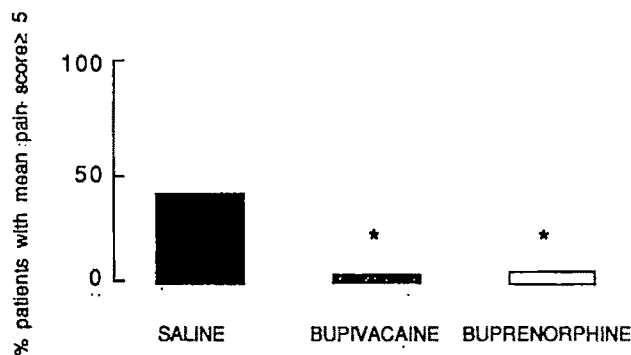


Fig 2. Percentage of patients in each group with mean pain score of 5 or more for the first 3 postoperative days. (* $p < 0.05$, intercostal bupivacaine and fixed-schedule buprenorphine compared with intercostal saline solution.)

as previously reported [7, 9, 10, 11], intercostal infusion of bupivacaine failed to provide complete analgesic effect. Possible explanations include the need to anesthetize higher intercostal nerves or to increase the dosage of bupivacaine [8].

Of major clinical importance is the absence of pulmonary complications in the group given the continuous intercostal blockade as compared with the group given intramuscular on-demand narcotics alone. This difference could be related to some discomfort caused by the indwelling catheter itself in the placebo group or, more likely, to the ability of patients in the group given the continuous intercostal blockade to comply with physical therapy because of good pain relief.

Effects on ventilatory function of bupivacaine-induced pain relief are less conclusive because reductions in lung volumes were similar in all three groups. However, many factors are involved in the development of restrictive impairment after thoracotomy [1, 2], and consequently the relative contribution of pain is uncertain. The extent of the lung resection is one important contributory factor. It likely accounts for the difference between our findings and those of Sabanathan [8], Toledo-Pereyra [10], Kaplan [11], and their associates, who reported improvement of postoperative pulmonary dysfunction after intercostal blockade. In their studies, however, thoracotomy was performed for both pulmonary and nonpulmonary operations, whereas all our patients underwent lung resection, which may have counteracted the beneficial effect of pain relief on respiratory function. Another cause of postoperative lung restriction that may be unaffected by pain relief is dysfunction of inspiratory muscles [12]. However, although respiratory muscle dysfunction has been shown to be unaffected by analgesia after upper abdominal operations [13], the effect of pain relief on inspiratory muscles has not been investigated after thoracic operations. In our study, decreases in lung volume were associated with parallel alterations in maximal inspiratory pressures, which reflect the strength of inspiratory muscles. Maximal inspiratory pressures were not correlated with pain scores, so reductions in maximal inspiratory pressures were similar in all the three groups.

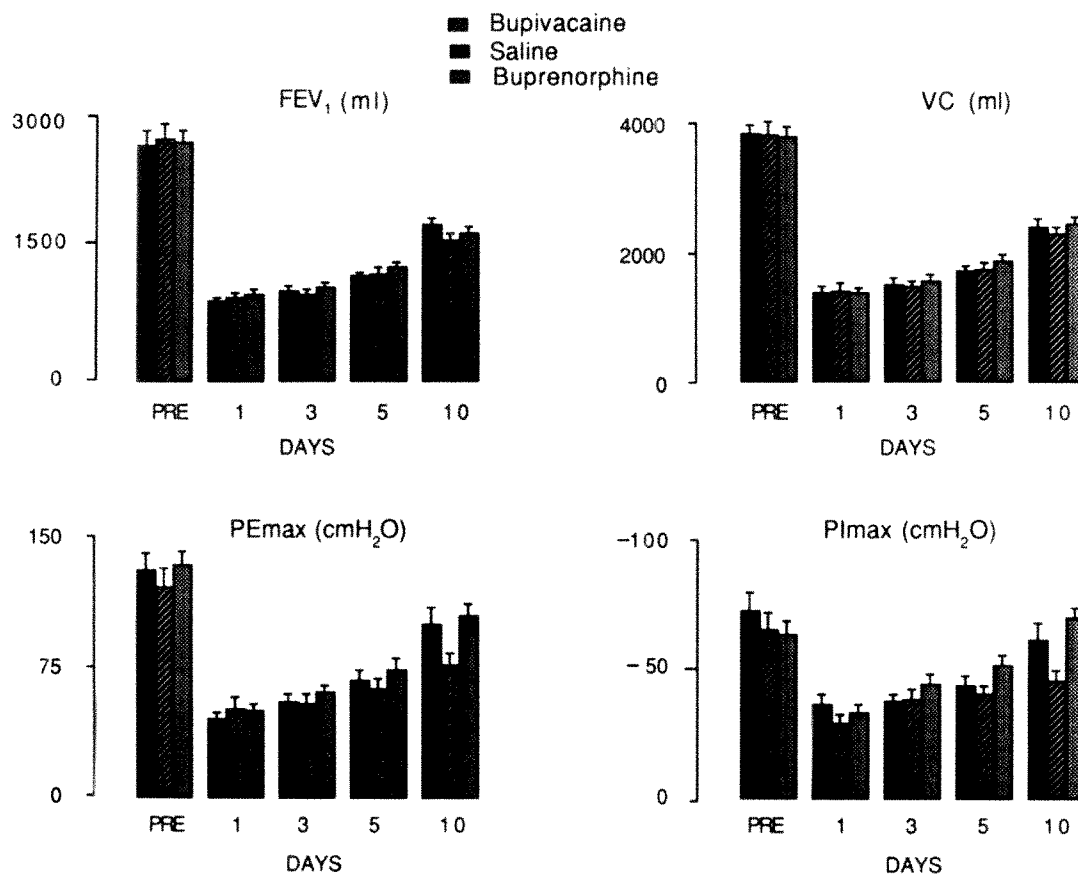


Fig 3. Absolute mean and standard error of the mean values of forced expiratory volume in 1 second (FEV₁), vital capacity (VC), and maximal static expiratory (PE_{max}) and inspiratory (PI_{max}) pressures in the three experimental groups over the study period. (PRE = preoperative values.)

We therefore suspect that pain relief-independent inspiratory muscle dysfunction may also account for our findings.

Continuous intercostal nerve blockade with bupivacaine through an indwelling catheter inserted during thoracotomy has several advantages over other methods of analgesia: (1) Intraoperative placement of the intercostal catheter reduces the risk of catheter malposition and pneumothorax associated with percutaneous insertion; malposition occurred in 3 of 52 patients in our early experience. (2) Although continuous intercostal bupivacaine appeared to have no benefit over fixed-schedule narcotics in pain relief, postoperative pulmonary complications, or pulmonary function, satisfactory analgesia was obtained with only a moderate amount of supplemental narcotics, thus minimizing the risk of narcotic-induced respiratory depression and cough reflex suppression. (3) The absence of sympathetic blockade, systemic hypotension, and respiratory depression are advantages of intercostal bupivacaine as compared with epidural bupivacaine. (4) Compared with the interpleural route, the intercostal route has been shown to provide comparable analgesia despite lower plasma bupivacaine levels [14]. Furthermore, in contrast to intercostal blockade, interpleural analgesia is not feasible after pneumonectomy. (5)

Finally, intercostal bupivacaine can be administered by the ward nursing staff, thus obviating the need for admission to high-dependency or intensive care units.

In conclusion, continuous intercostal blockade by bupivacaine is a safe, effective, easily administered form of analgesia after thoracotomy. This technique can be routinely used but is especially recommended for patients with impaired preoperative ventilatory function.

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REVIEW OF RECENT BOOKS

Tricuspid Atresia, Second Edition

Edited by P. Syamasundar Rao, MD

Mt. Kisco, NY, Futura, 1992

458 pp, illustrated, \$98.00

Reviewed by John H. Calhoun, MD

This monograph deals with tricuspid atresia in great detail. As such, it is not a book that every cardiovascular surgeon or cardiologist would need. However, it is a resource for those who do pediatric cardiac surgery and pediatric cardiology.

The text is divided into three sections. The first section, entitled "Background and the Basis," discusses in-depth historical features and classifications of the disease. Also, there is a complete chapter on demographic features of tricuspid atresia and an excellent review of the embryology. The conduction system is covered in an extensive chapter in a manner helpful to surgeons and cardiologists alike. Finally, classification is clarified by Dr Rao.

The second section is devoted to diagnosis. Because tricuspid atresia presents in a variety of manners, a clinical spectrum is developed in the first chapter of this section. Electrocardiographic features of the disease are reviewed in a separate chapter. The noninvasive evaluation of patients with tricuspid atresia is reviewed with attention to echocardiography, nuclear studies, and standard roentgenography. Included are chapters on exercise testing, cardiac catheterization, and angiography for tricuspid atresia. A chapter on left ventricular function is covered in

this portion of the text. The final chapter, "Natural History of Ventricular Septal Defects and Tricuspid Atresia," reviews this aspect of the disease and stresses the potential importance of the defect diagnostically.

The final section is devoted to the treatment and prognosis of patients with tricuspid atresia. A review of the treatment ranging from early pulmonary artery banding for initially overcirculated patients or shunt placement for undercirculated patients is made. Subsequent palliative operations including standard Glenn procedures, additional shunt operations, and bidirectional Glenn procedures are reviewed. Experimental work performed over the last 30 years on the physiology of the pulmonary circulation is reviewed in depth by Dr Sade. The Fontan operation is explored in detail, including its application in higher risk patients. A brief mention is made of the fenestration procedure and its possible role. An important set of chapters compile a vast amount of long-term follow-up on the Fontan procedure in patients with tricuspid atresia, including electrophysiologic, hemodynamic, and reference data toward sexuality and pregnancy in this subset of patients.

Dr Rao has compiled a wealth of information in a relatively short and readable text. This resource book is probably the most complete review of any congenital heart defect available. As such, it is recommended to all who treat patients with tricuspid atresia.

San Antonio, Texas

Homograft Aortic Root Replacement for Destructive Prosthetic Endocarditis

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Prosthetic aortic valve endocarditis with extensive destruction of the aortic root, annular abscess formation, and left ventriculoaortic discontinuity was seen in 3 patients, with aorta to left atrial fistula formation in 2. Homograft aortic root replacement with use of the anterior mitral leaflet of the aortic root to repair the fistula

was used successfully in all 3 patients. Their case reports are discussed to highlight the use of the homograft aortic root in these complicated cases, and to report the occurrence of aorto-left atrial fistula in prosthetic valve endocarditis.

(*Ann Thorac Surg* 1993;55:386-8)

Prosthetic valve endocarditis is a highly lethal, though fortunately uncommon, complication of cardiac valve replacement. Increasing surgical expertise and the high mortality with medical management have led to a more aggressive surgical-medical approach to prosthetic valve endocarditis. At times, the infective process may be extensive and destructive, and simple debridement and valve replacement may not be sufficient. Often one or more previous corrective surgical procedures have been performed, which produce a successively greater distortion of normal anatomy. This is exemplified by the patient with destructive aortic prosthetic valve endocarditis with aortic root abscess. A number of techniques to treat such patients have been described [1-5]. We describe our experience with one of these techniques: homograft aortic root replacement in 3 patients with complicated aortic prosthetic valve endocarditis.

Case Reports

Patient 1

A 26-year-old female patient was referred to the Cardiothoracic Surgical Unit of St Vincent's Hospital, Sydney, with a malfunctioning prosthetic aortic valve. Six years earlier she was operated on for acute streptococcal native aortic valve and root endocarditis. At that time, a prominent abscess was found in the region of the aorto-mitral continuity with complete destruction of the non-coronary cusp of the aortic valve. After aortic valve excision and debridement of the abscess, the abscess cavity was closed off with a Dacron patch. A 21-mm Björk-Shiley aortic mechanical prosthesis was used to replace the aortic valve.

The patient was asymptomatic for 8 months, after which aortic regurgitation developed due to prosthetic and left ventricular outflow patch dehiscence. The patient was reoperated on at this stage with excision and replace-

ment of the prosthetic patch and valve. Subsequently she underwent four open cardiac surgical procedures for prosthetic valvular and left ventricular outflow tract dysfunction over the next 3 years. Details of the various operative procedures have been outlined in a previous case report [6], the last open cardiac operation being a repair of a dehiscenced prosthetic St. Jude valve and Dacron patch.

In March 1988, 6 years after the first operation, she was seen with persisting paravalvular aortic regurgitation and hemolytic anemia and was taken for operation. Cardiopulmonary bypass was instituted with femoral arterial and right atrial cannulation. The partially detached St. Jude valve and Dacron patch were excised. A homograft aortic root replacement with reimplantation of the coronary arteries was carried out using freshly prepared antibiotic-sterilized aortic root homograft harvested from the recipient heart of a transplant patient in the unit. The postoperative period was uneventful. An echocardiogram showed a normally functioning aortic valve and left ventricle.

Patient 2

A 37-year-old man was admitted to a peripheral hospital with a 2-day history of fever, malaise, vomiting, headache, and rigors. His blood culture was positive for *Staphylococcus aureus*, and an echocardiogram showed vegetations on the posterior aortic valve leaflet. He was put on a regimen of appropriate antibiotics, but his fever continued. An aortic regurgitation murmur developed, and his condition deteriorated.

He was referred on July 20, 1989. He was found to be in extremis, febrile, dyspneic, and anemic with hepatosplenomegaly, raised jugular venous pressure, and multiple skin lesions with the skin peeling off his hands and feet. His electrocardiogram revealed a first-degree heart block.

After his condition failed to stabilize on intense medical therapy, he was taken for emergency operation, where 500 mL of sanguineous fluid was found in the pericardium. There was intense inflammation around the aortic

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root and, on exploration, frank pus was encountered posterior to the aorta. Cardiopulmonary bypass was instituted with topical hypothermia and cold blood potassium cardioplegic arrest of the heart. Aortotomy revealed a deformed bicuspid valve with thickened cusps, extensive inflammation of the whole aortic annulus, and an annular abscess on the posterolateral aspect in the fibrous curtain between the aortic valve and the anterior mitral leaflet related to the commissure between the left coronary and noncoronary cusps. The aortic valve was excised, and the valve ring and abscess cavity were debrided of all friable tissue. A 10-A Starr-Edwards prosthesis was inserted with obliteration of the abscess cavity using interrupted horizontal mattress sutures with subannular pledgets.

The patient came off bypass easily but remained febrile and tachycardic. A murmur developed on the fourth postoperative day, and an echocardiogram revealed a paravalvular leak and a communication between the aorta and the left atrium. The patient became progressively dyspneic and was taken back for operation on the seventh postoperative day. Cardiopulmonary bypass was instituted with femoral arterial and right atrial cannulation. A left ventricular apical vent was inserted and the heart arrested with cold blood cardioplegia given by direct coronary cannulation. Valve dehiscence with extreme disruption of the aortic annulus, especially posteriorly, related to the anterior mitral leaflet was found with a direct communication from the aorta to the left atrium in a paravalvular position. In view of this extreme and persisting infection, tissue destruction, left ventricular-aortic discontinuity and fistula formation, it was decided to avoid prosthetic material and to use a homograft aortic root. A cryopreserved 25-mm homograft aortic root was chosen. The homograft anterior mitral leaflet was used to repair and close off the aorto-left atrial fistula. The homograft aortic root was inserted with coronary artery reimplantation. The patient came off bypass well with minimal inotropic support of adrenalin. He made an uneventful recovery and was discharged after 6 weeks of antibiotic therapy.

Patient 3

A 37-year-old man was referred for prosthetic aortic valve endocarditis with vegetations and a complex posterior aortic root abscess with an aorto-left atrial communication. At age 21 years the patient had porcine aortic xenograft valve replacement for congenital aortic stenosis. This valve degenerated, and when the patient was 28 years old it required replacement by a bovine pericardial xenograft aortic valve. Four years later prosthetic valve endocarditis developed, which necessitated replacement with a St. Jude bileaflet aortic valve prosthesis. The patient was asymptomatic for the next 5 years. Then 6 weeks after a dental procedure with oral penicillin cover, a continuous low-grade fever developed with night sweats and headache. Clinically, splenomegaly and splinter hemorrhages in the nail bed of the toes were noted. On echocardiogram friable vegetations were seen on the aortic valve annulus with a complex posterior aortic root

abscess with aorto-left atrial communication. His blood was sent for culture and sensitivity and the patient was started on a heavy intravenous antibiotic cover. Repeated cultures were sterile, but his fever continued and he was referred in August 1991. In view of the continuous fever, the vegetations on the valve, and the abnormal communication, we decided to operate on him.

The femoral artery and vein were cannulated and midsternotomy performed. Cardiopulmonary bypass was instituted with an additional right atrial cannula for venous return. The heart was arrested by cold blood potassium cardioplegia instilled by direct coronary cannulation after a transverse aortotomy following aortic cross-clamping. The prosthetic valve was found to have friable vegetations on the annulus. The valve was excised. An abscess was found in the posterior part of the aortic root with a small (1 cm × 1 cm) fistula posteriorly below the annulus opening into the left atrium. The abscess cavity and fistula were debrided of all necrotic tissue. A size 22 cryopreserved aortic root homograft was selected with the anterior mitral leaflet attached to it. The homograft anterior mitral leaflet was sutured posteriorly so as to close off the fistula. The valve annulus was then sutured to the aortic root by implantation of the coronary arteries, which had been preserved and mobilized with a 3-mm cuff of surrounding aortic wall. The upper margin of the homograft was trimmed and sewn to the aorta. All the anastomoses were done with continuous 4-0 Prolene (Ethicon, Somerville, NJ). The patient made an uneventful recovery. A postoperative echocardiogram showed a normally functioning aortic valve and no fistula.

Comment

Prosthetic valve replacement for infective endocarditis has been accepted as a standard mode of treatment. There is, however, a tendency for prosthetic valve endocarditis to recur [7]. Mechanical prostheses have the highest rate of infection, homografts the least, and bioprosthetic valves an intermediate risk [8]. Also, in patients with associated aortic root abscess, aortic root destruction, and left ventriculo-aortic discontinuity, simple replacement of the infected prosthesis would not suffice and a more radical operation is required.

Several innovative surgical techniques have been applied to such cases. Symbas and associates [1] reported successful patch closure of the abscess and in situ valve replacement in 1 patient. Reitz and co-workers [2] described a method of translocation of the aortic valve, closure of the native coronary ostia, and saphenous vein bypass grafts to the coronary arteries on 4 patients, with success in 3. Frantz and colleagues [3] used composite prosthesis valve-woven Dacron tube graft reconstruction of the aortic root in 2 patients with success in 1. Kirklin and associates [4] reported successful treatment of 3 patients with infection of an aortic mechanical valve and annular abscess using an aortic valve homograft, the height of the homograft valve sinus being tailored to allow it to cover and exclude the abscess cavity.

Despite the successful results obtained with these tech-

niques, it may not be enough to replace the infected prosthesis and cover over the pus and infected material with pericardial or Dacron patches, as this leaves a pocket of infected material in situ with the risk of recurrence of infection, periprosthetic leak, and dehiscence of the prosthetic valve. Glazier and co-workers [5] have described 30 cases of prosthetic aortic valve endocarditis in which they used a technique of homograft aortic root replacement to avoid these problems. Eighty-one percent of the 21 hospital survivors remained free of major adverse effects (recurrence of endocarditis, need for reoperation, or death).

We have successfully used this technique in 3 patients with prosthetic valve endocarditis, annular abscess, left ventriculo-aortic discontinuity, and an aortic-left atrial fistula in 2 patients (patients 2 and 3). In patient 1, this procedure was required after six previous open cardiac procedures, whereas in patient 3, it was after two previous valve replacements. Conventional methods would most probably not have worked in these patients. The technique of homograft aortic root replacement allows excision of infected and necrotic tissue down to healthy noninfected tissue.

Two of our patients had extensive annular destruction with a fistula into the left atrium in the region of the commissure between the left and noncoronary cusps. The abscess and fistula were excluded from the left ventricle and outflow tract by suturing the leading edge of the anterior leaflet of the mitral valve to the inferior border of the abscess. The superior edge of the abscess was then sewn to the aortic annulus. The coronary arteries were then reimplanted and aortic continuity restored by end-to-end anastomosis of the homograft to the ascending aorta.

The homograft aortic root is a very durable structure, as shown by the results of studies involving large series of patients [9, 10] undergoing aortic root replacement for conditions in addition to prosthetic valve endocarditis, such as relief of various types of left ventricular outflow tract obstruction. The freedom from valve-related death at 5 years was $86\% \pm 6\%$ and freedom from valve-related death at 5 years was $96\% \pm 7\%$ [9]. The probability of freedom from valve failure in the homograft root has been estimated at about 92% at 10 years [11].

The aortic homograft immediately offers excellent hemodynamics of a totally competent valve and restores normal anatomy. This may not always be possible with free-hand homograft valve replacement in patients with distorted anatomy.

We believe that corrective operations in these difficult reoperations for prosthetic valve endocarditis should aim to be curative, radical, and safe, and a homograft aortic root with its inherent properties of durability and resistance to infection seems to be the operation of choice for these patients.

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Regulation of Acute Phase Response After Cardiopulmonary Bypass by Immunomodulation

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The object of this prospective, randomized trial was to study the dysregulation effects of cardiopulmonary bypass on the synthesis pattern of interleukin-1, tumor necrosis factor, and interleukin-6, which have been identified as the key mediators of acute phase response. In addition, the counterregulation achieved by administration of indomethacin, which blocks the downregulating mediator prostaglandin E_2 , or indomethacin combined with thymopentin, which enhances T-lymphocytic reactivity, was investigated. Sixty patients who had undergone open heart operations were included in the study. These patients were divided into three groups: group A ($n = 20$) received intravenous indomethacin alone, group B ($n = 20$) received both indomethacin and thymopentin, and group C ($n = 20$) served as control. In control

patients interleukin-1 and tumor necrosis factor synthesis were suppressed postoperatively. This effect was significantly counteracted by indomethacin with no further improvement by adding thymopentin. Interleukin-6 synthesis increased in all groups. Although indomethacin treatment alone had little effect on this phenomenon, additional administration of thymopentin significantly reduced elevated interleukin-6 synthesis. Corresponding differences in clinical outcome could not be detected due to small patient numbers. This study was, however, able to demonstrate that an immunomodulatory therapy can influence alterations in immune mechanisms after cardiopulmonary bypass.

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The uniform reaction of the human body to a variety of damage, eg, infections or trauma, is known as "acute phase response." Acute phase response is intended to counteract microbial invasion, localize tissue injury, and clear the body of debris. This is achieved by numerous reactions including activation of the complement cascade and cell-mediated immune system. Clinical symptoms include fever, anorexia, and synthesis of proteases known as acute phase proteins by hepatocytes [1, 2].

Acute phase response commonly results in a complete restoration of the injured tissue. However, if regulation of acute phase response becomes altered, chronic inflammation may be the outcome of too little activation and, in the case of too much activation, death. This dysregulation is caused by a shift in synthesis pattern of substances that mediate acute phase response [1, 2].

In recent years three different agents have been identified as key mediators of acute phase response: interleukin-1 (IL-1), tumor necrosis factor (TNF), and interleukin-6 (IL-6) [1-3]. Interleukin-1 is a cytokine produced mainly by activated immunoregulatory monocytes and macrophages [1-3]. Besides being involved in acute phase response, IL-1 induces production of other cytokines, for example, TNF from macrophages and IL-6 from fibroblasts. In addition, IL-1 represents an essential immuno-

stimulatory agent required for activation of cell-mediated immune response [1, 4, 5].

In many of these effects, IL-1 acts synergistically with TNF, which is produced primarily by macrophages [1, 2, 4, 6]. Tumor necrosis factor enhances production of cytokines, for example, interleukin-2 (IL-2) [4, 7] or IL-6 [2], but needs costimulation by other mediators, for example, IL-1, for this function. Therefore, TNF plays an essential part during activation and regulation of host response [7, 8].

On the other hand, TNF alone or in combination with IL-1 can induce shock [6], and there is evidence that TNF is the major factor responsible for lethal outcome of gram-negative sepsis [9, 10].

Interleukin-6 is another pleiotropic cytokine involved in acute phase response that may cause nearly every symptom of acute phase reaction [2]. It is produced by numerous cells, for example, immunocompetent T and B cells and by macrophages [2]. Interleukin-6 acts synergistically with IL-1 as a costimulator of enhanced T-cell proliferation [2, 5]. On the other hand, IL-6 may have some additional immunosuppressive effects, as IL-6 was found to be elevated in states of depressed immune response [6, 8, 11].

After open heart operations with cardiopulmonary bypass, patients frequently show fever, complement activation, elevated synthesis of acute phase proteins, and other symptoms that may be attributed to an activation of acute phase response [12]. However, instead of an enhanced recovery, patients are susceptible to infections, often

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Table 1. Preoperative Data^a

Variable	Group A (n = 20)	Group B (n = 20)	Group C (n = 20)	p Value
Mean age (y)	63.45 ± 7.19	62.48 ± 6.46	64.1 ± 6.79	NS
Male:female ratio	16:4	14:6	15:5	NS
Preoperative ejection fraction	0.61 ± 0.17	0.58 ± 0.17	0.64 ± 0.13	NS
Major coronary vessels compromised				
1	1	1	2	NS
2	4	8	7	
3	10	6	7	
Type of valvular disease				
Aortic	4	5	3	
Mitral	...	...	1	NS
Both	1	...	...	

^a Intergroup comparison of demographic data given as mean ± standard deviation.

NS = not significant.

caused by opportunistic microorganisms, which contribute substantially to multiorgan failure [13-15].

These data indicate that there may be a major imbalance within the regulation of acute phase response after cardiopulmonary bypass. The following prospective, randomized study was undertaken to investigate the kind and degree of alteration in synthesis pattern of the key mediators of acute phase response: IL-1, TNF, IL-6 [1-3].

In addition, the study attempted to determine whether immunomodulatory therapy could alleviate the dysregulation of acute phase response. For immunomodulation the cyclooxygenase inhibitor indomethacin, alone or in combination with the thymomimetic drug thymopentin, was used. Indomethacin blocks the synthesis of prostaglandin E₂ (PGE₂) which has been identified as one of the predominant mediators downregulating immune response [8, 16-20]. Therefore, suppression of PGE₂ synthesis by cyclooxygenase inhibition may offset the downregulating effects of PGE₂ on cytokine production.

Thymopentin has the same biological activities as the naturally occurring thymus hormone thymopoietin. It accelerates T-cell activation and T-cell recruitment [21] and may complement indomethacin in restoring or protecting host defense [22]. In a pilot study on cardiac surgical patients, thymopentin administration alone resulted in an encouraging restoration of T-lymphocytic response to antigenic stimulation but failed to restore T-cell receptor expression and cytokine synthesis [23]. Therefore, single-drug administration of thymopentin could not be expected to normalize acute phase response and was not tested.

Patients and Methods

Patient Population

This study was approved by the ethics committee of the Medical Faculty of the University of Munich. From November 1989 to October 1990, a total of 60 patients undergoing open heart operations, all older than 55 years and without evidence of a concomitant malignant or immunologic disease, were included. For the prospec-

tively randomized study they were divided into three subgroups: Group A (n = 20) was given indomethacin (Confortid; Dumex, Copenhagen, Denmark), 100 mg intravenously immediately after operation, and 50 mg three times daily until the fifth postoperative day. Group B patients (n = 20) received, in addition to indomethacin therapy, 50 mg of thymopentin (Timmunox; Cilag, Sulzbach, FRG) subcutaneously 2 hours preoperatively, as well as 48 hours and 96 hours postoperatively. Group C (n = 20) served as control.

All patients were blinded to treatment. There were 45 men and 15 women, who were 63.3 ± 6.8 years old. A total of 46 patients underwent coronary artery bypass grafting and 14 had valve replacement. (For further details see Table 1.)

Anesthesia was induced and maintained with etomidate (200 to 300 µg/kg), fentanyl (20 to 30 µg/kg), and nitrous oxide (50%) in oxygen. If necessary, isoflurane (0.4% to 1.5%) was added. One hundred to 200 µg/kg pancuronium was used as muscle relaxant. Ciprofloxacin (n = 16) and ceftriaxon (n = 44) were used for perioperative antibiotic prophylaxis.

Cardiopulmonary bypass was performed with nonpulsatile roller pumps and disposable bubble (n = 12) or membrane oxygenators (n = 48). The pump was primed with a standard electrolyte solution to which 50 mmol of sodium bicarbonate 8.4% and 2,000,000 U of aprotinin were added. After institution of cardiopulmonary bypass at a flow rate of 2.2 to 2.4 L · m⁻² · min⁻¹, the aorta was cross-clamped and cold crystalloid cardioplegic solution administered (either Kirklin's [n = 44] or Bretschneider's [n = 16] solution). Moderate hypothermia of 28°C was induced. Detailed operative data are listed in Table 2.

No statistical difference could be detected for data of Table 1 and Table 2.

Cell Preparation and Phenotyping

For leukocyte studies, 60 mL of peripheral blood was obtained in sterile heparinized tubes. The blood samples were diluted 1:2 in Hanks' buffered saline solution (Gibco, Grand Island, NY) with 2% penicillin-streptomycin. Pe-

Table 2. Operative Data^a

Variable	Group A (n = 20)	Group B (n = 20)	Group C (n = 20)	p Value
CPB duration (min)	76.3 ± 28.3	65.9 ± 24.3	68.1 ± 28.9	NS
X-clamp duration (min)	40.8 ± 17.7	36.0 ± 14.5	35.4 ± 13.3	NS
Lowest temp during CPB (°C)	28.1 ± 2.3	28.2 ± 2.3	28.3 ± 1.7	NS
Mean no. of distal coronary artery anastomoses	2.47 ± 0.72	2.33 ± 0.69	2.38 ± 0.59	NS
Type of artificial valve				
Mechanical valve	2	3	2	NS
Porcine bioprosthesis	3	3	2	

^a Intergroup comparison of operative data given as mean ± standard deviation.

CPB = cardiopulmonary bypass; NS = not significant; X-clamp = aortic cross-clamp.

ripheral blood mononuclear cell (PBMC) isolation was carried out immediately by standard Ficoll-Hypaque density gradient centrifugation at 1,500 rpm and 40°C for 35 minutes. After the cells were resuspended with 15% fetal calf serum (Gibco) cell counts were performed with a hemocytometer using 0.1% trypan blue exclusion as a test of viability, which always exceeded 95%. Untreated PBMCs were adjusted to a concentration of 10×10^6 PBMCs/mL.

Interleukin-1 and Tumor Necrosis Factor Assay

Interleukin-1 as well as TNF production in PBMCs was generated by culturing the cell suspension at a cell concentration of 5×10^6 PBMCs in 5-mL culture tubes in the presence of highly purified lipopolysaccharide (*Corynebacterium parvum*; Wellcome Inc, London, UK) at a final concentration of 1 µg/mL at 37°C and 6% carbon dioxide. After 24 hours, supernatants were collected and stored at -80°C until assayed. Interleukin-1 and TNF were measured using a radioimmunoassay for human TNF and IL-1 as previously described [24, 25]. These assays used alloantisera raised in rabbits against the respective human cytokine and radioiodinated cytokine as the tracer.

Interleukin-6 Assay

Peripheral blood mononuclear cells were stimulated with lipopolysaccharide to generate IL-6 synthesis preferentially in monocytes. To generate IL-6 production preferentially in T-lymphocytes PBMCs were cultured at a cell concentration of 4×10^6 PBMCs/mL in the presence of highly purified phytohemagglutinin at a final concentration of 2.5 µg/mL at 37°C and 6% carbon dioxide. After 48 hours, supernatants were collected and stored at -80°C until assayed.

Interleukin-6 was measured employing the MTT assay [26] as described previously [27] using a murine hybridoma cell line (7TD1) that grows only in the presence of IL-6.

Statistical Analysis

Statistical analysis was done with the use of variance analysis and χ^2 test for intergroup analysis. Student's paired *t* test was used for intragroup comparison. A *p* value less than 0.05 was considered significant. The results are expressed as mean ± standard error of the mean, unless otherwise indicated.

Results

Operative Mortality and Morbidity

During the early postoperative period of 30 days, 2 patients died, giving an operative mortality of 3.3%. Both had undergone coronary artery bypass grafting. One patient had been given indomethacin (group A), the other belonged to the control group C. Both died due to septic multiorgan failure, death occurring on postoperative day 10 and day 19, respectively. In both patients pneumonia was the first site of infection to be detected 5 and 4 days before death, respectively. Bacteriologic investigation revealed *Staphylococcus epidermidis* and *Candida albicans* as causative pathogens.

The early morbidity rate was 7% (4/60). One group A patient survived a sepsis that also originated from the lungs. *Staphylococcus epidermidis* was once again identified as the causative microorganism.

Patients who received the combined immunomodulatory therapy produced no evidence of systemic infections. However, one local infection originating from the sternum (day 6) was seen. Another sternum osteitis was found in the control group C (day 9) as well as an aseptic sternal dehiscence (day 16).

No significant difference could be found between the three groups with respect to operative mortality and morbidity.

Immunologic Investigations

INTERLEUKIN-1. The synthesis of IL-1 by PBMCs after lipopolysaccharide challenge decreased in control patients (group C) from a preoperative baseline value of 1.19 ± 0.32 ng/mL to 0.82 ± 0.14 ng/mL on day 1 and remained depressed until the end of the observation period (Fig 1). On day 7, synthesis of IL-1 was 0.78 ± 0.11 ng/mL.

Conversely, in patients treated with indomethacin (group A) there was a substantial increase in IL-1 synthesis on day 1 to 2.66 ± 0.68 ng/mL versus 1.17 ± 0.31 ng/mL preoperatively. On the following days synthesis of IL-1 decreased but remained elevated at 1.86 ± 0.6 ng/mL (day 3), 1.94 ± 0.54 ng/mL (day 5), and 1.93 ± 0.49 ng/mL (day 7).

The additional administration of thymopentin (group B) resulted in nearly the same synthesis pattern of IL-1 as in group A patients. Again an increase in IL-1 synthesis on day 1 to 2.28 ± 0.63 versus 1.1 ± 0.16 ng/mL preopera-

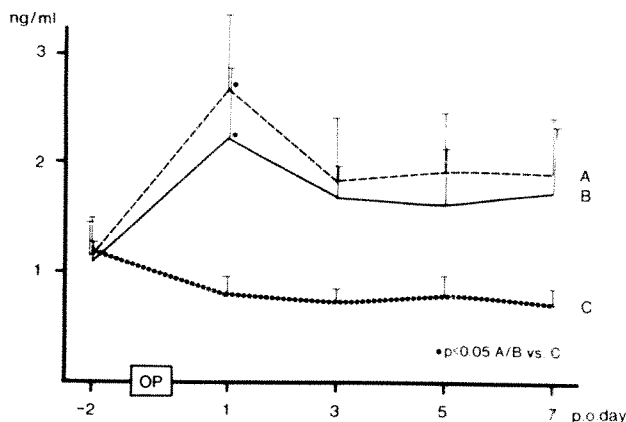


Fig 1. Interleukin-1 synthesis during the first 7 postoperative (p.o.) days after open heart operation (OP) as compared with preoperative baseline values. Data are given for patients receiving indomethacin (A), patients receiving indomethacin combined with thymopentin (B), and controls (C). Dots indicate values that are significantly different comparing groups A and B with control group C.

tively was followed by a decrease in IL-1 on the following days to values still elevated at 1.7 ± 0.3 ng/mL (day 3), 1.62 ± 0.5 ng/mL (day 5), and 1.78 ± 0.6 ng/mL (day 7).

No significant difference were observed when comparing the results within each group. An intergroup comparison, however, showed a significantly higher IL-1 synthesis on day 1 in groups A and B versus group C.

TUMOR NECROSIS FACTOR. The results obtained for this mediator of acute phase response paralleled those found for IL-1 synthesis. Again the results for group C patients (Fig 2) decreased from 1.65 ± 0.17 ng/mL preoperatively to 1.09 ± 0.27 ng/mL on day 1 and remained depressed to 0.91 ± 0.19 ng/mL until day 7.

Administration of indomethacin resulted in a substantial increase in TNF synthesis with a peak on day 1 (2.94 ± 0.74 ng/mL). During the following days TNF synthesis slowly decreased, reaching preoperative baseline values (1.74 ± 0.31 ng/mL) on day 7 (1.61 ± 0.26 ng/mL).

Combined therapy with indomethacin and thymopentin lead to an additional increase in TNF synthesis with a peak on day 1 (3.13 ± 0.77 ng/mL) and day 3 (3.19 ± 0.9 ng/mL). Even at the end of the observation period substantially higher values (2.18 ± 0.57 ng/mL) compared with preoperative baseline values of 1.71 ± 0.3 ng/mL were found.

No significant difference could be found when comparing the values within each group. An intergroup comparison showed a significant higher TNF synthesis for group A and B patients versus group C patients on days 1, 3, and 5 (see Fig 2).

INTERLEUKIN-6. Results of IL-6 synthesis (Fig 3a) differed from those observed in IL-1 and TNF production. All patients showed a substantial increase in IL-6 synthesis by monocytes after lipopolysaccharide challenge, reaching a peak on day 3 (group A, $4,024 \pm 165$ U/mL versus $2,107 \pm 113$ U/mL preoperatively; group B, $2,852 \pm 842$ U/mL versus $1,125 \pm 74$ U/mL preoperatively; group C, $3,508 \pm$

217 U/mL versus $1,533 \pm 63$ U/mL preoperatively), and then slightly decreased until day 7. On day 7, however, IL-6 synthesis was still almost twofold higher compared with preoperative baseline values in all groups (group A, $3,440 \pm 147$ U/mL; group B, $2,207 \pm 226$ U/mL; group C, $2,943 \pm 201$ U/mL).

On each day investigated, group C patients showed the highest and group B patients the lowest increase in IL-6 synthesis whereas group A patients had intermediate results. This is not clearly visible on Figure 3a due to the differences in baseline values. However, no statistically significant difference in intragroup or in intergroup comparison could be detected except for IL-6 synthesis on day 1, which was significantly lower for group B patients compared with group A patients.

Interleukin-6 synthesis after phytohemagglutinin stimulation, ie, synthesis mainly by T-lymphocytes (Fig 3b), showed a pattern similar to that after lipopolysaccharide challenge. Interleukin-6 production increased in all groups with a peak on day 3 (group B, $1,878 \pm 440$ U/mL versus $1,608 \pm 331$ U/mL preoperatively) and day 5 (group A, $2,388 \pm 544$ U/mL versus $1,585 \pm 337$ U/mL preoperatively; group C, $2,544 \pm 557$ U/mL versus $1,507 \pm 303$ U/mL preoperatively). On day 7, IL-6 synthesis was still elevated in group C to $2,356 \pm 475$ U/mL, in group A to $2,107 \pm 486$ U/mL, and in group B to $1,770 \pm 407$ U/mL. During the whole observation period group C patients again showed the highest IL-6 values, whereas the lowest increase in IL-6 synthesis was found in group B patients. These differences gained statistical significance on day 3 and day 5, when IL-6 synthesis in group B was significantly lower than in group C.

Comment

Previous studies have demonstrated that cardiopulmonary bypass, in addition to the operation, alters immunoreactivity, whereas anesthesia has only little effect on host response after a cardiac operation [28, 29]. The question,

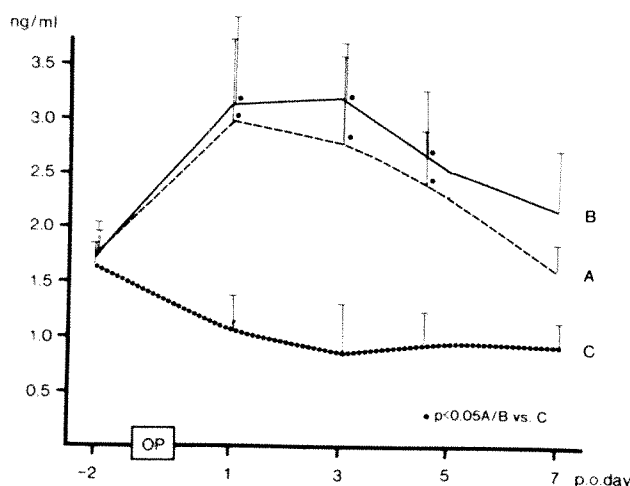


Fig 2. Tumor necrosis factor synthesis during the first 7 postoperative (p.o.) days after open heart operation (OP). Dots indicate results that are significantly different comparing groups A and B with control group C.

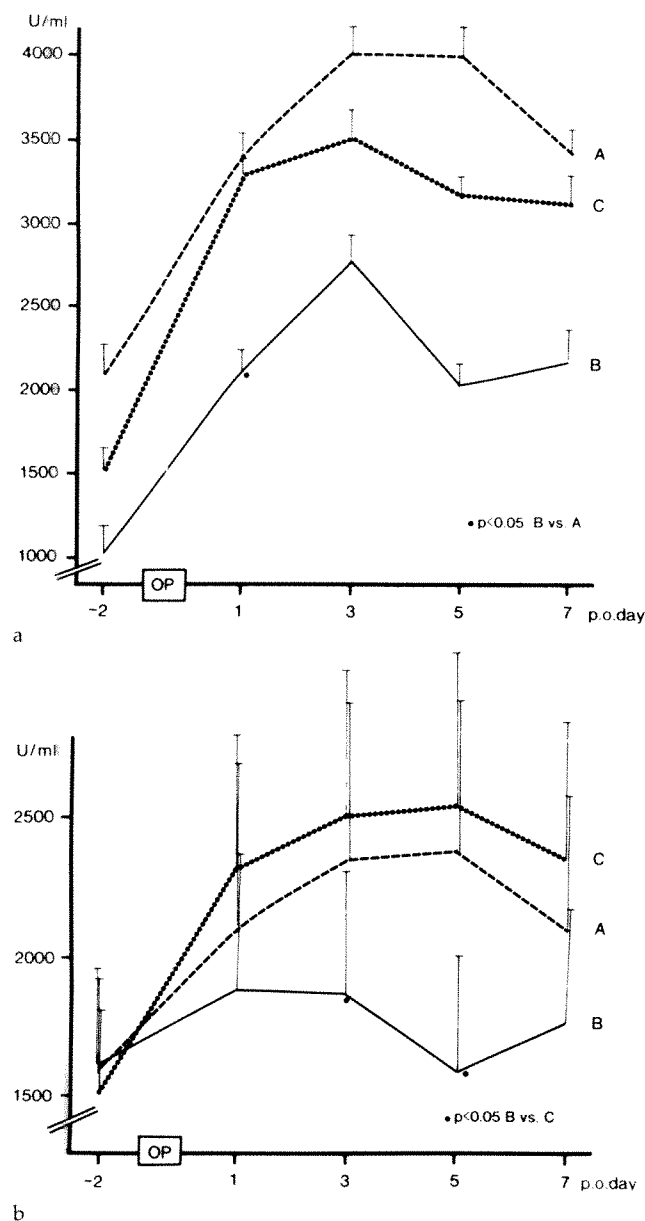


Fig 3. (a) Interleukin-6 synthesis by monocytes after stimulation with lipopolysaccharide during the first 7 postoperative (p.o.) days after open heart operation (OP). Dot indicates the only result that is significantly different between groups A and B. (b) Interleukin-6 synthesis by T-lymphocytes after stimulation with phytohemagglutinin. Dots indicate the results that are significantly different between groups B and C.

which part of the extracorporeal circulation is responsible for these alterations, cannot be answered with the available data. Most likely, the foreign surfaces of the bypass circuit represent the predominant factor that alters immune response by inappropriate activation [12, 30].

The results of this study suggest that cardiopulmonary bypass results also in an activation of acute phase response: IL-6 is upregulated, IL-1 and TNF synthesis are downregulated in untreated patients (group C). In several animal and other human studies the same changes in synthesis patterns of IL-1, TNF, and IL-6 were found and

related to a depression of host response [8, 11, 31-34]. A downregulation of IL-1 and TNF synthesis has been demonstrated in an animal model of hemorrhaged mice [8]. It was associated with an impaired antigen presentation and major histocompatibility complex class II expression by antigen presenting cells, which are essential for the activation of immune response. These results corroborate the hypothesis that depressed IL-1 and TNF synthesis might have immunosuppressive effects.

Highly elevated IL-6 concentrations are frequently found in patients with burns or infections [6, 31, 32]. The upregulation of IL-6 synthesis in T cells is very likely the result of an intracellular shift from IL-2 synthesis to IL-6 synthesis [11]. Interleukin-1 is known to be downregulated in immunocompromised patients [33]. The decrease in IL-1 synthesis of monocytes has been attributed to an intracellular shift from IL-1 to production of PGE_2 , which is an inhibitor of IL-1 synthesis [34]. Interleukin-1 and IL-2, however, are the two essential cytokines mediating forward regulation of cell-mediated immune response [1, 2]. A depression of IL-1 and IL-2 synthesis therefore implies a suppression of cell-mediated immune response.

All the information and data derived from the present study support the depression of cell-mediated immune response by decreased IL-1 and TNF synthesis. An impaired host response leaves the patient in a partially immunocompromised state that might facilitate infections during the early postoperative course.

The key substance mediating immunosuppressive alterations of host response is PGE_2 , which is known to downregulate IL-1 and TNF synthesis [8, 16, 18-20]. In addition, PGE_2 impairs cell-mediated immune response by reducing, for example, T-cell blastogenesis, IL-2 synthesis, IL-2 receptor expression, and cytotoxicity by activated T cells [17-19]. All these alterations were observed after an adequate operative or accidental trauma had initiated monocytic production of PGE_2 . Prostaglandin E_2 blockade by cyclooxygenase inhibition with indomethacin should counteract PGE_2 -mediated dysregulation of acute phase response. For this reason indomethacin was given after the operation to counteract excessive host response after cardiopulmonary bypass.

Ertel and associates [8] were, in fact, able to demonstrate in an animal study that administration of the cyclooxygenase inhibitor ibuprofen resulted in an upregulation of IL-1 and TNF synthesis and a downregulation of IL-6 production. In our study, administration of the cyclooxygenase inhibitor indomethacin was able to counteract completely the downregulating effects of PGE_2 on IL-1 and TNF synthesis, whereas there was little effect on IL-6 synthesis.

Another agent was therefore required to complete the immunobalancing effects of indomethacin. Because indomethacin contrasuppresses downregulating effects, it seemed sound to add a substance to this treatment that enhances forward regulation, for example, a thymomimetic drug such as thymopentin [21]. The rationale for preoperative administration of thymopentin was to augment host defense mechanisms before operation, as host defense is known to be depressed in elderly patients even without trauma or operation [23, 35]. Interleukin-6 pro-

duction by monocytes and lymphocytes was, in fact, substantially reduced by addition of thymopentin compared with indomethacin alone or with controls. Any possible effect on IL-1 and TNF synthesis was not demonstrable, but production of these mediators had already been corrected by indomethacin treatment.

Although the results of immunologic screening demonstrated significant differences when regulation of acute phase response with immunomodulation was compared with controls, these differences had only a slight impact on the clinical outcome. The number of patients included in this study was obviously too small to demonstrate a significant clinical effect of immunomodulation. Further investigations with more patients will be necessary to achieve this. However, our study was able to demonstrate that immunomodulation can change alterations in the synthesis pattern of cytokines and mediators that are essential for the regulation of acute phase response.

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Cardiac Preconditioning Does Not Require Myocardial Stunning

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Efforts to minimize the deleterious effects of intraoperative myocardial ischemia-reperfusion (I/R) injury have been primarily directed at optimizing cardioplegic solutions and altering reperfusion conditions. Classically, myocardial I/R has been associated with cardiac mechanical dysfunction ("stunning"). Recently, we reported an α_1 -adrenergic receptor-mediated mechanism of paradoxical myocardial protection against I/R insult induced by a prior episode of transient ischemia, a phenomenon known as "ischemic preconditioning." Myocardial stunning resulting from transient ischemia has previously been associated with ischemic preconditioning, prompting intuitively negative bias against the clinical application of this phenomenon. The purpose of this study was to determine whether transient ischemia of insufficient duration to cause prolonged mechanical dysfunction (stunning) can induce favorable cardiac preconditioning. Isolated-perfused rat hearts were allowed to equilibrate for 8 minutes and were then subjected to either 2 minutes of global, normothermic transient ischemia or 2 minutes

of 50 $\mu\text{mol/L}$ phenylephrine infusion. A stabilization period of perfusion lasting 10 minutes after the termination of transient ischemia or phenylephrine infusion was followed by a standard I/R challenge (20 minutes of global, normothermic ischemia; 40 minutes of reperfusion). Ventricular function (measured as developed pressure in millimeters of mercury) recovered rapidly after transient ischemia such that no impairment was present before the subsequent standard I/R challenge. Phenylephrine treatment was associated with no residual inotropy before I/R challenge. Control hearts were subjected only to the standard I/R challenge after an initial 20-minute equilibration period. After reperfusion control hearts exhibited 54.4% recovery of initial left ventricular developed pressure. Transient ischemia- and phenylephrine-preconditioned hearts recovered 84.4% ($p < 0.01$) and 82.4% ($p < 0.01$), respectively. We conclude that the benefits of myocardial preconditioning do not require the deleterious effects of myocardial stunning.

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Efforts to reduce myocardial mechanical dysfunction after cardiac surgical procedures requiring cardioplegic arrest have been primarily directed at optimizing cardioplegic solutions [1] and, more recently, manipulating reperfusion conditions [2, 3]. Nevertheless, inotropic and mechanical support are still occasionally required to prevent morbidity and mortality from stunned myocardium [4]. Recent investigations have revealed the presence of intrinsic myocardial systems with exciting therapeutic implications that markedly enhance tolerance to myocardial ischemia/reperfusion (I/R) injury.

Murry and associates [5] have described paradoxical protection against prolonged ischemic insult afforded by a prior transient ischemic episode, a phenomenon known as "ischemic preconditioning." Classically, the preconditioning ischemic event has been associated with myocardial mechanical dysfunction ("stunning") persisting into the onset of the more extensive ischemic insult. We [6] have previously reviewed the associations between I/R, myocardial stunning, and cardiac preconditioning. Recent investigations [7] into the mechanism of ischemic precon-

ditioning have dissociated stunning as a causal factor; however, preconditioning has not previously been reported in the absence of stunning [8]. Induction of intrinsic protective mechanisms against I/R is clinically appealing. The intuitively negative bias, however, inherent to prophylactically stunning the heart before a cardiac operation limits the utility of this phenomenon. We have recently reported that ischemic preconditioning is mediated by α_1 -adrenoceptor stimulation via norepinephrine release induced by transient ischemia [9]. This study was undertaken (1) to determine whether acute cardiac preconditioning may occur in association with transient ischemia of sufficient brevity to allow rapid and complete functional recovery before a more extensive I/R insult and (2) to examine whether the α_1 -adrenoceptor-mediated mechanism of preconditioning can be exploited by exogenous pharmacologic agents, obviating the need for transient ischemia.

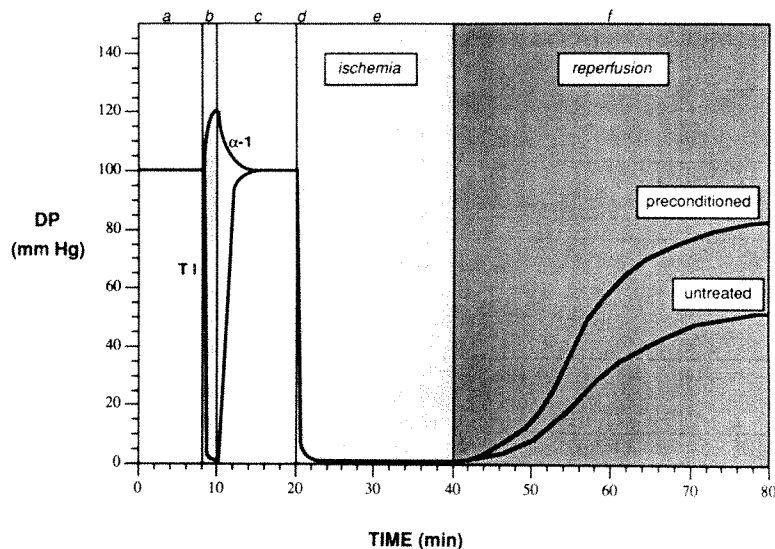
Material and Methods

Male Sprague-Dawley rats (325 to 350 g; Sasco Inc, Omaha, NE) were fed a standard diet and acclimated in a quiet quarantine room for 2 weeks before experimentation. The animal protocol was reviewed and approved by the Animal Care and Research Committee, University of

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Fig 1. Schematic diagram of experimental protocol depicting representative courses of untreated and preconditioned hearts. All hearts were maintained a total of 80 minutes. Control hearts were perfused unperturbed for 80 minutes (a-f). Transient ischemia control hearts and phenylephrine control hearts were equilibrated 8 minutes (a) before 2-minute stimulation (b), then perfused unperturbed for 70 minutes (c-f). Untreated hearts were equilibrated 20 minutes (a-c) before the standard ischemia/reperfusion challenge (d-f). After corresponding preconditioning with transient ischemia (TI) or phenylephrine (α -1) hearts were stabilized 10 minutes (c) before standard ischemia/reperfusion challenge. (Phases: a = pretreatment equilibration [8 minutes]; b = preconditioning stimulation [2 minutes]; c = posttreatment stabilization [10 minutes]; d = ventricular failure at onset ischemia; e = continued ischemia [d + e = 20 minutes]; f = reperfusion [40 minutes].)



Colorado Health Sciences Center. All animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" (NIH publication No. 85-23, revised 1985). Unless otherwise noted all chemicals and reagents were obtained from Sigma Chemical Company, St. Louis, MO.

Preparation of Isolated Rat Heart

The isolated, crystalloid-perfused rat heart used in our laboratory has been previously described [10, 11]. Rats were anesthetized (sodium pentobarbital, 60 mg/kg, intraperitoneally) and heparinized (500 units, intraperitoneally). Hearts were rapidly excised, placed in iced oxygenated perfusate, mounted on a modified Langendorff apparatus, and perfused (70 mm Hg) with Krebs-Henseleit solution (1.2 mmol/L Ca^{2+} , 4.7 mmol/L KCl, 25.0 mmol/L NaHCO_3) in a retrograde fashion at the aortic root. A gas mixture (92.5% O_2 , 7.5% CO_2 ; S-070 oxygenator [Shiley Inc, Irvine, CA]) was used achieving a perfusate oxygen tension of 450 mm Hg, carbon dioxide tension of 40 mm Hg, and pH of 7.4. A water-filled latex balloon was inserted into the left ventricle through the left atrium and adjusted to a left ventricular end-diastolic pressure of 6 mm Hg. Pacing wires were fixed to the pulmonary outflow tract, and hearts were paced at 360 beats/min (pacer off during ischemia and drug infusions). Hearts that could not be paced at 360 beats/min were discarded. Ventricular developed pressure (DP) was continuously recorded with a direct pressure amplifier (Gould Electronics, Houston, TX). A three-way stopcock above the aortic root was turned to create global ischemia, during which the heart was placed in a degassed perfusate-filled organ bath maintained at 38°C.

Experimental Design

All experimental and control groups consisted of 5 animals. All hearts were kept on the perfusion apparatus for 80 minutes. A control group was perfused without interruption for the full 80 minutes to ensure stability of the

preparation. Experiments consisted of an equilibration period of 8 minutes and a subsequent preconditioning stimulus of 2 minutes, followed by a 10-minute period of perfusion (Fig 1). Hearts were then subjected to 20 minutes of global, normothermic ischemia and 40 minutes of reperfusion, our standard I/R challenge [10, 11]. Hearts that were not preconditioned (control I/R group) were allowed to equilibrate uninterrupted for 20 minutes followed by the standard I/R challenge.

Transient Ischemia

After the mandatory 8-minute equilibration period, pacing was discontinued and perfusion was interrupted for 2 minutes. Hearts (TI+I/R group) were placed in the 38°C organ bath during transient ischemia (TI). After the transient ischemic period, hearts were allowed to recover for 10 minutes (the poststimulus equilibration period), before subjecting them to the standard I/R challenge. A control group (TI control) was preconditioned but not subjected to the standard I/R challenge to assess for functional stability over the remainder of the protocol.

Pharmacologic Preconditioning

After 8 minutes of equilibration, phenylephrine (PE) dissolved in normal saline solution was infused for 2 minutes with a Harvard pump through a port above the aortic root such that a 50- $\mu\text{mol/L}$ solution was delivered into the coronary arteries. We have previously demonstrated preconditioning with this dose [9]. Hearts were not paced during drug infusion. After a 10-minute postinfusion stabilization period, this group (PE+I/R group) was subjected to the standard I/R challenge. A control group (PE control) was similarly treated with PE without the subsequent I/R challenge to assess for residual positive inotropy or deleterious drug effects.

Ventricular Failure in Ischemia

The time (in seconds) from the onset of the standard I/R challenge to complete ventricular failure in preconditioned

tioned heart (TI and PE) and untreated heart was measured from the continuous tracing of DP.

Statistical Analysis

Values for cardiac DP were compared by analysis of variance. Post hoc Scheffe's *F* test was applied to detect significant differences at a confidence level of *p* less than 0.01. Mean DP at the end of the initial 8-minute equilibration period in the standard I/R group was compared with the mean DP immediately preceding the standard I/R challenge. To assess for the presence of myocardial stunning or residual inotropy resulting from the preconditioning stimulus, identical comparisons were made in the TI and the PE groups, respectively. Recovery (expressed as percent recovery $\pm$ standard error of the mean) after the standard I/R challenge in the I/R, TI, and PE groups was calculated for individual hearts by dividing the DP at the end of reperfusion (see Fig 1, *f*) by the DP at the end of the initial 8-minute equilibration period (see Fig 1, *a*). Efficacy of preconditioning was evaluated by comparing the post-reperfusion recovery of the I/R group with the TI+I/R and PE+I/R groups, again using analysis of variance and applying post hoc Scheffe's *F* test with a confidence level of *p* less than 0.01. The mean times (seconds $\pm$ standard error of the mean) to complete ventricular failure at the onset of sustained ischemia for TI-treated, PE-treated, and untreated hearts were compared using analysis of variance and applying post hoc Scheffe's *F* test with a confidence level of *p* less than 0.05.

Results

The control group subjected to 80 minutes of continuous perfusion exhibited a loss of ventricular function of 8%. Figure 2 shows that a single 2-minute episode of transient normothermic ischemia (preceded by 8 minutes of equil-

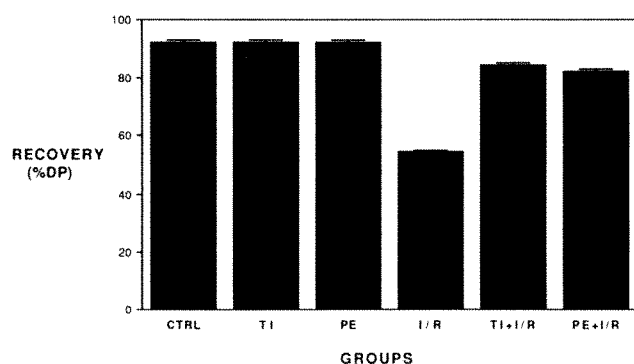


Fig 2. Functional recovery with preconditioning: Left ventricular function after 80 minutes expressed as percent of initial left ventricular developed pressure (DP). Transient ischemia (TI) and 50 μ mol/L phenylephrine (PE) without the standard ischemia/reperfusion (I/R) challenge neither augment nor impair final function compared with control (CTRL). Hearts preconditioned with either TI or PE before standard I/R challenge (20 minutes of ischemia, 40 minutes of reperfusion) demonstrate improved functional recovery compared with unpreconditioned hearts.

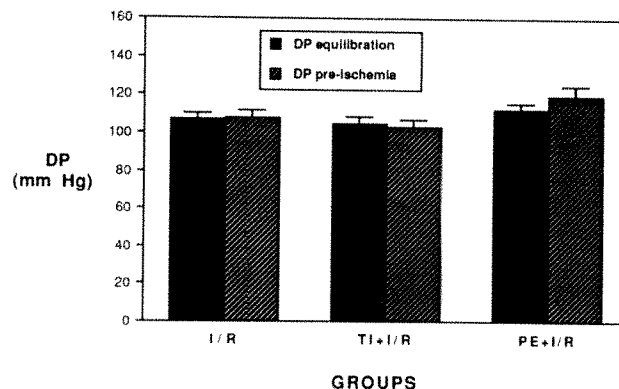


Fig 3. Pretreatment function compared with posttreatment function before standard challenge: After transient ischemia (TI) there was complete return of function by the end of the stabilization period after preconditioning (see Fig 1, *c*). Hearts pretreated with phenylephrine (PE) before ischemia/reperfusion challenge (I/R) had a residual increase of 7.4 mm Hg ($p < 0.05$) at the corresponding time. Left ventricular developed pressure (DP) in hearts submitted to I/R alone was unchanged during the equilibration period (Fig 1, *a-c*). Thus, beneficial preconditioning does not require deleterious myocardial stunning.

ibration) and followed by 70 minutes of perfusion has no effect on ventricular function compared with control. Similarly, no deleterious effects were observed with a 50- μ mol/L PE infusion over 2 minutes. Additionally, no residual inotropic effect was observed in this group. The standard I/R challenge resulted in a postreperfusion recovery of $54.4\% \pm 3.3\%$ of initial ventricular function in untreated hearts. In contrast, preconditioning resulted in improved recoveries of $84.4\% \pm 1.0\%$ ($p < 0.01$) and $82.4\% \pm 3.2\%$ ($p < 0.01$) in the TI+I/R and PE+I/R groups, respectively, compared with standard I/R challenge alone.

Figure 3 demonstrates that no ventricular functional deficits (ie, stunning) persisted in the TI+I/R group before the onset of the standard I/R challenge. Rapid recovery of function occurred after the TI stimulus. The PE+I/R group exhibited no residual inotropy at the end of the postinfusion stabilization period. We conclude that myocardial dysfunction can completely recover after TI while myocardial preconditioning against a sustained ischemic insult is induced. Furthermore, equivalent cardiac preconditioning by exogenous α_1 -adrenoceptor stimulation can be achieved without any functional impairment. Finally, the time from the onset of the standard I/R challenge to complete ventricular failure was no different in untreated hearts compared with preconditioned hearts (I/R, 130 ± 4.5 seconds; TI+I/R, 131 ± 10.0 seconds; PE+I/R, 126 ± 10.1 seconds; $p > 0.05$). We conclude that a transient ischemic time insufficient to cause functional stunning, but sufficient to precondition, does not induce more rapid ventricular failure at the onset of sustained ischemia.

Comment

Myocardial stunning was originally defined mechanically as fully reversible prolonged ventricular dysfunction after

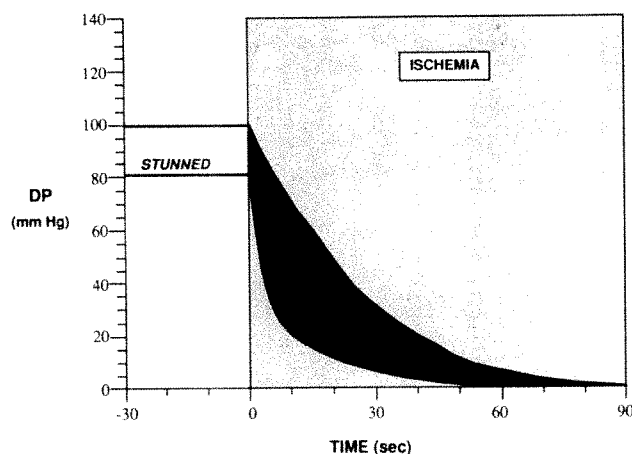


Fig 4. Hypothetical depiction of ventricular failure during ischemia: Theoretically, stunned heart should fail more rapidly than normal heart at the onset of ischemia. The area under each curve is theoretically proportional to energy expended during futile contractions early in ischemia. Reduced energy expenditure in stunned heart could result in net energy preservation (represented by the shaded area) during sustained ischemia contributing to preconditioning. We observed no difference in the failure rates of preconditioned and nonpreconditioned heart. Similarly, left ventricular developed pressure (DP) before the standard challenge were not different in these groups.

I/R insult of insufficient magnitude to cause cellular necrosis [4]. In both experimental models and clinical correlates of this phenomenon, contractile dysfunction persists an order of magnitude longer than the inciting ischemic event. Stunned heart is characterized by hypocontractility and reduced diastolic compliance that return to normal over a time span inversely related to the duration of the ischemic event. Intuitively, one might expect successive ischemic insults interposed by reperfusion to cause cumulative injury. Surprisingly, Murry and colleagues [5] demonstrated that a period of brief ischemia paradoxically renders myocardium resistant to the effects of subsequent ischemia, a phenomenon they termed "ischemic preconditioning." Their original canine model of ischemic preconditioning against subsequent prolonged I/R injury employed a transient ischemic time of 15 minutes, which by itself produced stunning lasting up to 3 days. These stunned hearts demonstrated markedly reduced infarct size after sustained ischemia compared with control. This observation led to the hypothesis that myocardial stunning may be causally associated with ischemic preconditioning [12, 13].

Murry and co-workers [13] have demonstrated that TI retards adenosine triphosphate depletion and slows both glycogenolysis and anaerobic glycolysis during a subsequent prolonged ischemic episode, yielding a net preservation of energy stores in preconditioned heart. At the onset of ischemia, ventricular contractions weaken rapidly (see Fig 1, *d*) with a transition to futile contractions followed by complete mechanical failure (see Fig 1, *e*). These investigators proposed that stunned myocardium subjected to a second episode of ischemia might exhibit more rapid mechanical failure with fewer futile contrac-

tions, therefore expending less energy during initial ischemia resulting in a net energy conservation in preconditioned heart (Fig 4) [7]. In our model we found no quantifiable difference in the rate of ventricular failure in preconditioned heart compared with untreated heart. Furthermore, if stunning is inexorably associated with preconditioning, the magnitudes of the two phenomena should be directly related, and the temporal course of each should coincide. That is, increased stunning might enhance preconditioning, and the preconditioning effect should persist concurrent with ventricular dysfunction. However, the severity of stunning has not correlated with favorable preconditioning. Miura and colleagues [14] demonstrated no correlation between the magnitude of stunning and the extent of resultant protection. Similarly, the duration of ischemic preconditioning does not correlate with the duration of mechanical dysfunction. Murry and associates [7] have noted marked attenuation of the protection afforded by ischemic preconditioning well before any recovery of mechanical function occurs. Miura and colleagues [15] likewise found that the protective effect of ischemic preconditioning lasted only 30 minutes, a time much less than that required for mechanical recovery from stunning in their model.

In this study we have demonstrated that ischemic preconditioning and myocardial stunning can be further dissociated. We observe that TI of sufficient brevity to allow complete mechanical functional recovery before the sustained ischemic insult effectively preconditions against the latter insult. Other investigators have shown that ventricular function of isolated rat heart returns within 90 seconds after a single 5-minute episode of global normothermic ischemia [16]. The time course for recovery after TI in our model was roughly equivalent to the duration of TI. This differs from classic models of stunning, in which recovery requires a time period much longer than the ischemic event. Furthermore, the time from the onset of ischemia to complete ventricular failure in preconditioned hearts (TI or PE) did not differ from control, suggesting that futile energy expenditure was similar in all groups.

The mechanism of myocardial stunning is unresolved; however, a leading hypothesis invokes toxic oxygen radicals elaborated upon reperfusion [6, 17]. This hypothesis is supported by numerous studies that demonstrate improved mechanical function achieved with free radical scavenger administration [18]. An early report suggested that free radical production at reperfusion may be a causative factor in preconditioning [12]. Administration of superoxide dismutase and catalase attenuated preconditioning in 50% of treated animals; however, the lack of an effect in the remaining animals could not be explained. A more recent investigation demonstrated no attenuation of ischemic preconditioning with superoxide dismutase and catalase administration [19]. Support for a mechanistic link between myocardial stunning and ischemic preconditioning is therefore lacking.

One could argue that a transient ischemic time of 2 minutes constitutes transient stunning. First, investigations of high-energy phosphate content in typical models of stunned heart have found adenosine triphosphate

reductions of 50% with slow repletion over a period of days [4]. However, other investigators have demonstrated that ischemia of 5 minutes' duration in isolated rat heart resulted in comparatively less adenosine triphosphate depression [16], and with reperfusion phosphocreatine overshoot coincided with the rapid return of ventricular function. Nevertheless, total adenosine triphosphate content remained depressed after recovery. Second, several investigators have shown that catecholamine stimulation can unmask contractile reserve in stunned heart [20-22]. We have previously demonstrated that endogenously released norepinephrine is increased after TI [9]; therefore, the rapid recovery after our 2-minute TI could reflect inotropic support from endogenous norepinephrine. However, endogenous catecholamine release is transient. Thus, catecholamine-dependent functional support should also be temporary, and a decline in mechanical function would be expected within the time frame of our model. The group that was allowed uninterrupted perfusion for 70 minutes after TI demonstrated no functional deterioration compared with control, indicating that the prompt return of ventricular contractility after TI is not catecholamine-dependent.

Recovery of myocardial function may precede metabolic recovery in stunned heart [17]. In the present study myocardial high-energy phosphate were not assessed. However, in an in vivo porcine model, other investigators have clearly demonstrated enhanced recovery of high-energy phosphate in heart preconditioned with transient ischemic durations sufficient to cause stunning [23]. Furthermore, in previous work we found that the improved functional recovery of preconditioned heart paralleled enhanced high-energy phosphate repletion during reperfusion [9]. Metabolic recovery was not different in hearts preconditioned with TI or norepinephrine. We believe that similar results would be found with PE.

Recently, we have determined that ischemic preconditioning is mediated by α_1 -adrenoceptor stimulation caused by norepinephrine release from myocardial sympathetic neurons [9]. Endogenous catecholamine release in response to ischemia as observed in our model should also occur with transient ischemic durations sufficient to cause significant stunning. Clearly, preconditioning by pharmacologic means does not require ventricular dysfunction. Conceivably, exogenous α_1 -adrenoceptor stimulation could be analogous to stunning. However, other investigators have recently attributed ischemic preconditioning to the activation of adenosine A_1 receptors by adenosine released during TI [24]. The α_1 and adenosine A_1 mechanisms may be interrelated [6].

This study demonstrates that the benefits of cardiac preconditioning do not require the deleterious effects of myocardial stunning in isolated rat heart. Subsequent in vivo validation of these findings would encourage the clinical application of preconditioning. The ability to simulate ischemic preconditioning by pharmacologic manipulation of myocardial receptors, without incurring antecedent functional impairment, has significant clinical implications. The scheduled nature of I/R stress sustained during cardiac operations should allow for the prophylac-

tic exploitation of pharmacologically induced preconditioning. The healthy myocardium of donor heart makes heart transplantation an ideal setting for the therapeutic application of this phenomenon. Further investigation of the signaling events and intracellular effectors of preconditioning may yield even more suitable applications for clinical cardiac preconditioning.

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INVITED COMMENTARY

Heart muscle differs from other tissues of the mammalian organism because of its high energy requirements to support contraction. Because its energy needs far exceed its adenosine triphosphate stores (human heart utilizes about 35 kg of adenosine triphosphate per day, whereas its adenosine triphosphate stores amount to not more than 300 mg, ie, a 100,000-fold difference!), the heart relies on the continuous supply of oxygen and substrates to fuel oxidative phosphorylation. The intricate network of metabolic control through intermediary metabolism of substrates provides a responsive system to the energy needs of the heart. Under normal conditions there is tight, beat-to-beat coupling between substrate utilization, oxygen consumption, and cardiac work. Consequently, ischemia results in an almost instantaneous decline in contractile function.

Protection of the ischemic and reperfused myocardium is a prerequisite for successful cardiac operation and transplantation. For the most part this protection is afforded by cardioplegic solutions, often in combination with hypothermia. Conventional methods reach their limits in patients with compromised contractile function before operation, in patients requiring prolonged periods of ischemic arrest, and in situations calling for prolonged ex vivo storage of donor hearts for cardiac transplantation. Investigators have therefore recently turned to new mechanical, pharmacological, or metabolic measures to protect the jeopardized myocardium. Of these methods, ischemic preconditioning (a term used to describe enhanced tolerance to prolonged periods of ischemia after

one or more brief periods of ischemia followed by reperfusion) has received most of the attention.

Although the mechanism of ischemic preconditioning is not clear, several important aspects of the phenomenon are now coming to light. The present study by the Denver group concludes that, although ischemic preconditioning is not associated with stunning, it can nevertheless be mimicked by α -adrenergic stimulation. This is an intriguing concept. However, critics may argue that "pharmacological preconditioning" has not brought us any closer to understanding the mechanism of the phenomenon. A positive study in rat hearts is not sufficient reason to test the same hypothesis in patients, and more work is clearly needed. The results should furthermore be considered in the wider context of other preischemic manipulations found to enhance ischemia tolerance such as increasing myocardial glycogen ("glycogen loading") or raising the levels of free radical scavengers.

We begin to see that there are many facets to preconditioning. As investigators turn their attention to the myocardium itself, we can hope that a unified, clinically useful concept on preconditioning may soon emerge. The present study is a step in the right direction.

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Hyperbaric Oxygenation for Arterial Air Embolism During Cardiopulmonary Bypass

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The incidence of systemic air embolism during cardiopulmonary bypass is estimated to be 0.1%. However, the vast majority of instances are unreported and quietly ignored. The result may be disability or death. The control of air embolism obviously lies in prevention. The definite and specific treatment of this complication is hyperbaric oxygen. We report 6 patients referred to our institute because of air embolism during cardiopulmonary bypass. Of the 4 patients in whom hyperbaric oxygen therapy was delayed for 17 to 20 hours, 2 showed

partial neurological improvement, as opposed to the success of hyperbaric oxygen therapy in the 2 patients in whom the delay was minimal. We conclude that as soon as the proposed open heart operation has been completed and there is an indication that air embolism has occurred, the patient should be treated with hyperbaric oxygen as quickly as possible, even before neurologic manifestations of cerebral ischemia appear.

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Arterial air embolism during cardiopulmonary bypass can result in serious brain damage or fatality. The incidence of this complication is estimated to be 0.1% [1, 2]. Currently more than 3,500 operations with cardiopulmonary bypass are performed annually in Israel, so that 3 patients with air embolism may be expected. Despite improvements in equipment and technology, these accidents still occur, demanding quick and accurate diagnosis and efficient therapeutic measures.

The immediate management includes Trendelenburg position, hypothermia, steroids, anticoagulants, oxygen, and volume expansion [3, 4]. Retrograde perfusion has been suggested as a means of decreasing the amount of air obstructing the cerebral circulation [5, 6], yet only 47% of the gas was recovered by this modality in an animal model [4]. The definite and specific treatment of this complication is hyperbaric oxygen (HBO). It has been concluded that every heart surgeon should ascertain the nearest hyperbaric facility and should adopt a contingency plan to be followed in the event of air embolism [7, 8].

We report 6 patients referred to our institute since January 1985 because of arterial air embolism during cardiopulmonary bypass. In each case diagnosis was made by the referring surgeon, based on his suspicion that a considerable amount of air had entered the systemic circulation during the operation. The patients were treated in a large multiplace hyperbaric chamber. The chamber is the only hyperbaric referral facility in Israel, and so these 6 patients reflect the total national clinical experience.

Case Summaries

Six patients were referred with a diagnosis of air embolism. Of the 4 patients who had undergone coronary artery bypass grafting, 2 had undergone additional surgical procedures. The fifth patient had undergone closure of an atrial septal defect, whereas aortic valve replacement had been carried out in the sixth.

Two of the patients were referred immediately on completion of the operation, which made it possible to commence HBO therapy with a delay of only 2 to 3 hours. These 2 patients made a complete recovery. In the remaining 4 cases, the surgeons preferred to wait and observe the impact of the embolism on the recovery process. Only when normal recovery was not observed the following day were these patients referred for HBO. This resulted in a considerable delay in the commencement of therapy. Two of the 4 patients died, 1 was left with severe neurological impairment, and 1 was left with a mild motor deficit in one leg. In 5 cases, a modified version of the US Navy treatment table 6A was used (Fig 1). One patient was given 90 minutes of oxygen at 2.8 atmospheres absolute. The main clinical data are summarized in Table 1.

Comment

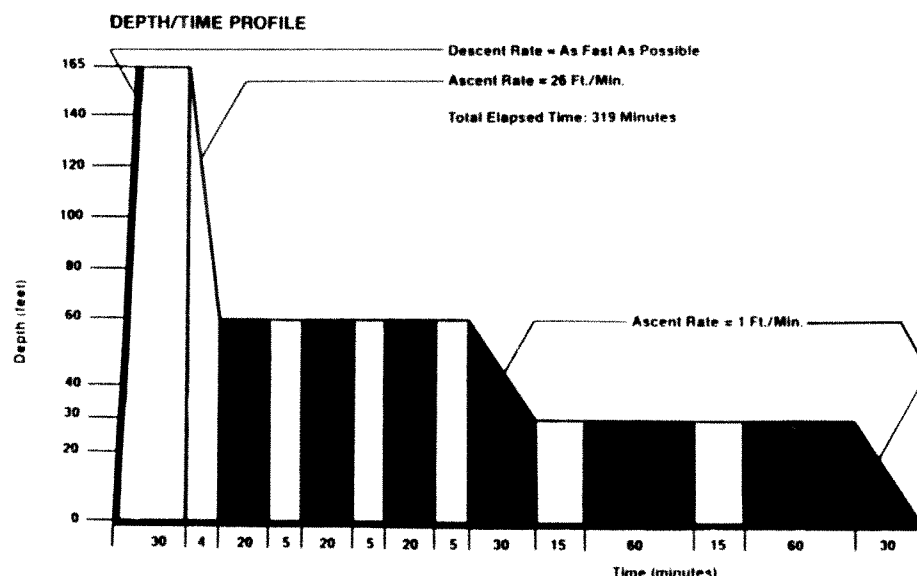
Arterial air embolism accompanying cardiopulmonary bypass may result in disability or even death. In a survey of 349 cardiac surgeons [1], the incidence of arterial air embolism was estimated to be 0.1%, but its true incidence seems to be higher [7]. The vast majority of instances are unreported and quietly ignored, mainly due to a fear of litigation.

According to the statistics of Stoney and associates [1], there were 429 instances of arterial air embolism in 374,819 cardiopulmonary bypass operations (0.11%). Of these, 61 resulted in disability (14.2%), and 92 patients

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Fig 1. US Navy Treatment Table 6A. This graph indicates the pressure (depth in feet) inside the hyperbaric chamber at any given time, the rate at which pressure is increased or reduced, and the gas breathed during the various stages of the treatment. Solid areas denote intervals of exposure to pure oxygen, and open areas intervals of exposure to air. The table is used by us in a modified form. To increase the oxygen partial pressure during the first 30 minutes of therapy, a 50%/50% nitrogen/oxygen mixture is introduced instead of air at this critical stage.



(21.4%) died of the complication, which can occur at the onset of perfusion, during perfusion, or on resumption of cardiac function [7].

A number of causes of air entry into the bypass circuit have been documented, including rupture of arterial lines and connectors, oxygenator defects, arterial reservoir run dry due to insufficient venous return, and sudden acceleration of a roller pump [9, 10].

The control of air embolism lies in prevention. It is incumbent upon each open heart team to be prepared to deal with the situation should it arise. Guidelines for this and other emergency procedures should be established and practiced by the perfusionist team. The management of gross air embolism should include the following [11]:

1. The arterial pump is immediately stopped and the venous line clamped.
2. The patient is placed in a steep head-down position.

3. The aortic cannula is removed and the arterial circuit purged of air.
4. The arterial cannula is connected to the venous line to facilitate retrograde perfusion. Alternatively, the atrium can be cannulated separately.
5. Retrograde perfusion at a flow of 1 to 2 L/min and at a temperature of 20°C is carried out with the flow directed up the superior vena cava. This is continued for a few minutes with the suction system being used to retrieve blood exiting from the aortotomy.
6. The anesthetist exerts pressure on the carotid arteries, and retrograde perfusion is continued until the arterial system is cleared of air. In extreme cases, retrograde perfusion through the inferior vena cava may also be required.
7. Standard bypass is resumed with hypothermia, and attention is turned toward removing any air that may have entered the coronary system, by pharmacological

Table 1. Main Clinical Data

Patient No.	Age (y)	Sex	Operation	HBO Therapy	Time to HBO (h)	Main Symptoms	Outcome
1	53	M	CABG	6A ^a	17	Coma; mechanically ventilated; no response to pain; hypotonia	No response; severe impairment
2	62	F	CABG + carotid endarterectomy	2.8 ATA, 90 min	18	Coma; mechanically ventilated; hypotonia	No response; died
3	57	M	CABG + mitral valve replacement	6A ^a	20	Coma; mechanically ventilated; responsive to pain	Improved
4	4	F	Closure of ASD	6A ^a	2	Coma; mechanically ventilated	Complete recovery
5	55	M	CABG	6A ^a	20	Coma; mechanically ventilated; no response to pain; pupils dilated	No response; died
6	70	F	Aortic valve replacement	6A ^a	3	Coma; mechanically ventilated; pupils reactive to light	Complete recovery

^a Modified

ASD = atrial septal defect; ATA = atmospheres absolute; CABG = coronary artery bypass grafting; F = female; HBO = hyperbaric oxygen; M = male.

elevation of the perfusion pressure and small-needle puncture of the distal coronary system.

8. The operative cardiac procedure is completed as quickly as possible.

Rewarming is carried out slowly to a core temperature of 35°C, and bypass is completed in the usual fashion. The patient is ventilated on 100% oxygen. The value of steroid therapy is unproven, but it may be beneficial. Hyperosmolar and diuretic therapy is mandatory and ideally should be monitored with intracranial pressure.

Hyperbaric oxygen is considered a specific therapy for air embolism because it is based on the mechanical compression of air bubbles according to Boyle's law: the volume of a gas is inversely proportional to the pressure to which it is exposed [8, 12]. Hence compression to 6 atmospheres absolute will reduce the size of an intravascular bubble to one sixth of its original volume, which is 55% of its original diameter. This reduction helps relieve the vascular obstruction and restores perfusion. Concomitantly, HBO reduces the blood nitrogen partial pressure, increases the gradient between the bubbles and the blood, and accelerates bubble resorption. In addition, HBO both increases ischemic brain tissue oxygenation and reduces brain edema by vasoconstriction [7].

Winter and colleagues [13] and Tomatis and co-workers [8] indicated that HBO therapy may be lifesaving even after a delay as great as 11 hours, before irreversible brain damage. Mader and Hulet [14] predicted that HBO therapy may be useful in the treatment of cerebral air embolism even if this therapy is delayed more than 24 hours after embolization. This is in accord with our experience [15].

Because minor air embolism is so common and the immediate clinical impact seems, erroneously [16], to be negligible, the cardiac surgeon is reluctant to refer the patient for HBO therapy, even when a major air embolus is seen entering the arterial circulation. Only when the patient remains comatose some hours later is HBO therapy considered.

Because our chamber is the only hyperbaric referral facility in Israel, our experience represents the total number of patients referred for HBO therapy since 1985. According to statistics from the Israel Ministry of Health, in the course of these 6 years 16,332 operations with cardiopulmonary bypass were performed. According to Stoney and associates [1] the estimated number of patients with air embolism during this time would be 16. We believe, then, that the 6 patients described reflect only a fraction of the patients who should have been referred for HBO. It might be mentioned that ground transportation using a mobile intensive care unit proved safe in all 6 cases, and caused no further morbidity. The multiplace chambers in most hyperbaric centers can offer continuous intensive care during HBO therapy, as mechanical ventilators and monitoring equipment are available.

Definite conclusions cannot be drawn from the 6 patients described, but of the 4 patients in whom HBO therapy was delayed for 17 to 20 hours, only 1 showed significant neurologic improvement (patient 3), as opposed to the success of HBO therapy in patients 4 and 6, in whom the delay was minimal.

We conclude that massive arterial air embolism should be treated with HBO as quickly as possible, even before neurologic manifestations of cerebral ischemia appear.

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Noninvasive Hemodynamic Assessment of the Internal Mammary Artery in Myocardial Revascularization

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Using transthoracic B-mode imaging and Doppler spectrum analysis it was found that the luminal diameter of the internal mammary artery and its hemodynamics were not significantly different among 15 preoperative patients (64 ± 10 years) who underwent myocardial revascularization using the left internal mammary artery and young and older control groups (25 ± 3 years and 61 ± 9 years, respectively). These data indicate that older age does not significantly adversely influence the degree of intimal thickening and compliance in the internal mammary artery. Doppler spectrum analysis of the internal mammary artery in the patients who were operated on revealed conversion from a triphasic systolic waveform preoperatively to a unidirectional combined systolic/

diastolic waveform at 1 week and 2 and 6 months postoperatively, characterized by a significant increase in the diastolic blood flow velocity and a significant decrease in the systolic blood flow velocity and the pulsatility and resistance indices. This study indicates that transthoracic B-mode imaging and Doppler spectrum analysis are promising noninvasive techniques in the preoperative assessment of internal mammary artery morphology and physiology. In addition, Doppler spectrum analysis can also be used in the long-term serial assessment of the internal mammary artery conduit after myocardial revascularization.

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During the last decade there has been a steep increase in the rate of myocardial revascularization procedures using the internal mammary artery (IMA). Preoperative angiographic and intraoperative ultrasonic imaging of the coronary arteries, as performed in some centers, provides primarily morphologic information about the IMA [1-4]. Intraoperative Doppler spectrum analysis of blood flow velocities in coronary artery bypass grafts and coronary arteries may provide valuable information with regard to intraoperative graft function and coronary blood flow characteristics, but fails to provide insight in the preoperative and postoperative hemodynamics of the IMA [5-10]. Such data may be important with regard to preoperative assessment of suitability of the IMA as a coronary artery bypass graft and postoperative assessment of graft function. In our search for a reliable noninvasive diagnostic technique for preoperative and postoperative hemodynamic assessment of the IMA in myocardial revascularization we used an echo-Doppler apparatus in which a B-mode real-time two-dimensional imaging system is combined with a pulsed Doppler unit.

The objectives of this study were (1) investigation of the clinical applicability of transthoracic B-mode ultrasonic imaging and Doppler spectrum analysis in the preoperative and postoperative morphologic and functional assess-

ment of the IMA as a conduit in myocardial revascularization and (2) investigation of the anticipated postoperative change in hemodynamic pattern in the IMA.

Material and Methods

The study group, which has been described previously [11], consisted of 15 patients, between 45 and 80 years of age (mean age, 64 ± 10 years), who all underwent elective myocardial revascularization using the left IMA and additional reversed saphenous vein aortocoronary grafts. Postoperatively, none of the patients was on vasoactive medication. The postoperative hematocrit ranged from 0.35 to 0.41.

Transthoracic B-mode images and Doppler spectra were obtained (or an attempt was made to obtain them) from all left IMAs (that were all used as bypass conduits) and from all right (nonused) IMAs. Both techniques were applied preoperatively, at the end of the first postoperative week; and at 2 and 6 months postoperatively. After informed consent was obtained, postoperative angiograms of the IMA conduit were made in 5 patients as a morphologic reference for the postoperative ultrasonic assessment of graft function.

Similar to the patient group, in two control groups transthoracic B-mode imaging and Doppler spectrum analysis were applied to investigate both IMAs. The first control group consisted of 20 young, healthy volunteers,

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with ages ranging from 22 to 30 years (mean, 25 ± 3 years). The second control group consisted of 20 age-matched (range, 45 to 76 years; mean, 61 ± 9 years) and sex-matched patients who had been admitted for noncardiac diseases and who were subjected to the same noninvasive measurements.

For all echo-Doppler examinations the scanner head was positioned at the first intercostal space with the patient in the supine position. Guided by the B-mode image, the Doppler sample volume was placed in the IMA in such a way that the ultrasound beam had an angle of 60 ± 7 degrees to the axis of blood flow. An echo-Doppler apparatus (Toshiba SSA 270A duplex scanner, Tokyo, Japan) with a 5-MHz linear array transducer was used for the color B-mode imaging and for the recording of the Doppler spectra. In all patients, both preoperatively and postoperatively, the cross-sectional diameter of the IMA was measured (or we attempted to measure it) with B-mode imaging. Subsequently, Doppler signals from the IMA were recorded. Our technique of Doppler spectrum analysis has been described previously [11-13]. Three parameters were calculated to describe the shape of the Doppler spectrum curves, namely, the maximum frequency, the end-diastolic frequency, and the mean frequency [14]. The pulsatility and resistance indices, which both are dimensionless figures, were derived by combining different parameters [11, 15-18].

All IMA harvesting and intraoperative measurements were performed by an observer who was not aware of the results of the preoperatively measured IMA diameter. The IMA was mobilized with its pedicle from the first or second rib to a point 1 to 3 cm distal to the bifurcation into the superior epigastric and musculophrenic branches and subsequently divided distally. Low-current electrocoagulation was used for harvesting, and Hemoclips (Edward Weck and Co, Research Triangle Park, NC) were applied to large branches. The external IMA diameter was measured as proximal as possible (at the first or second intercostal space) by use of a sterile caliper and was correlated with the preoperatively measured luminal IMA diameter.

Values are expressed as mean values $\pm$ standard deviation. The differences between two means were compared by paired and unpaired Student's *t* tests. The criterion for statistical significance was a *p* value of 0.05 or less.

Results

Suitable B-mode images of the IMA could be obtained in all 15 preoperative patients and in all control individuals (Fig 1). Postoperatively this was achieved in all nonused IMAs and in 7 of 15 IMA conduits (47%). Therefore, the postoperatively measured luminal diameters of the IMA conduits were not used for further analysis. In addition to measurements of the luminal IMA diameter, it was possible to identify wall thickening and vessel calcification, although such phenomena were observed in only 2 patients and in none of the control individuals. There were no significant differences in the luminal IMA diameter among the three groups (Table 1). In the patient group the

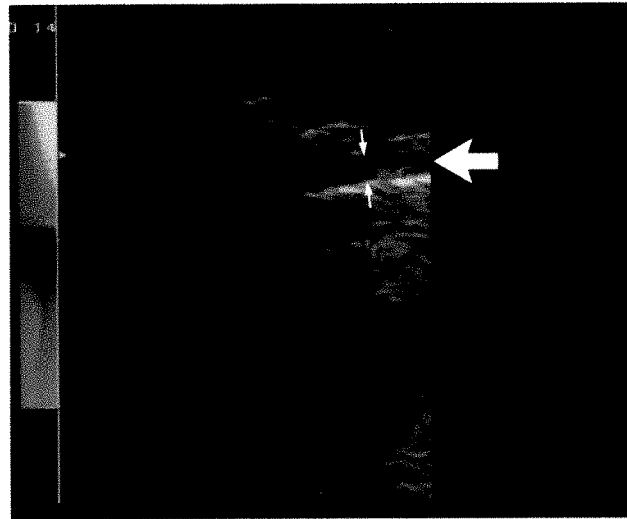


Fig 1. Preoperative B-mode image of internal mammary artery (large arrow) at level of the first intercostal space. There is no sign of local intimal thickening. The luminal diameter at the site of the red mark (between small arrows) is 3.6 mm. The blue mark indicates the internal mammary vein.

preoperatively noninvasively measured luminal IMA diameter (3.3 ± 0.3 mm) correlated well with the intraoperatively measured external diameter (4.2 ± 0.5 mm), considering the fact that the width of the IMA wall is approximately 300 to 400 μ m [19].

Adequate Doppler spectra of the IMA could be obtained in all preoperative patients and control individuals. Postoperatively adequate Doppler spectra were obtained in all nonused IMAs and in 14 of 15 IMA conduits (93%). Figure 2 shows typical examples of the blood flow velocity waveforms as observed in the control groups and the preoperative patients. In all individuals a triphasic waveform was obtained with a large systolic peak followed by small reversed and diastolic flow components. There were

Table 1. Doppler Spectrum Parameters and Luminal Diameter as Measured in Both IMAs in Young Control Group (A) and Control Group of Similar Age as Patient Group (B), and in Right IMA in the Preoperative Patient Group^a

Parameter	Control (A)	Control (B)	Patients
No. of IMAs	40	40	15
Mean age (y)	25 ± 3	61 ± 9	64 ± 10
F _{max} (Hz)	$2,026 \pm 250$	$1,809 \pm 317$	$1,984 \pm 402$
F _{dia} (Hz)	209 ± 75	155 ± 118	135 ± 106
Adv (Hz)	503 ± 97	528 ± 146	469 ± 107
RI	0.90 ± 0.04	0.91 ± 0.07	0.93 ± 0.06
PI	3.9 ± 1.4	4.0 ± 1.6	4.4 ± 1.5
Preop diameter (mm)	3.2 ± 0.4	2.9 ± 0.6	3.3 ± 0.3

^a Values are shown as mean $\pm$ standard deviation.

Adv = mean frequency of curve; F_{dia} = end-diastolic frequency of advancing curve; F_{max} = maximum frequency of advancing curve; IMA = internal mammary artery; PI = pulsatility index; RI = resistance index.

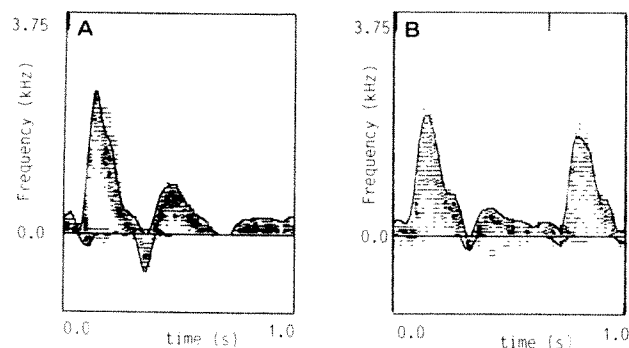


Fig 2. Typical Doppler spectra as obtained from the internal mammary artery in (A) control individual of similar age as patients who underwent myocardial revascularization with internal mammary artery and (B) patient who underwent myocardial revascularization with internal mammary artery (preoperative situation). Mark at top indicates beginning of systole.

no significant differences in the five Doppler spectrum parameters among the three groups (Table 1).

Postoperatively 12 patients were in New York Heart Association functional class I, and 3 patients were in class II. In all 14 patients in whom adequate postoperative Doppler spectra of the IMA conduit were obtained the preoperative triphasic waveform had been converted into a combined systolic/diastolic waveform. In 12 patients an early systolic peak was followed by a lower diastolic peak (Fig 3), whereas in 2 patients a different waveform was observed, consisting of an early systolic peak followed by abrupt approximation of the blood flow velocity to zero and a large diastolic component that exceeded the systolic component (Fig 4). In all 14 patients the postoperative hemodynamics were characterized by a significant increase in the end-diastolic and mean frequencies and a significant decrease in the maximum frequency and the pulsatility and resistance indices (Table 2). These changes were maximal at 2 months postoperatively and then gradually declined, but remained significant at 6 months postoperatively. Postoperative angiography in 5 patients showed normal IMA conduits and widely patent IMA-coronary artery anastomoses, with proximal IMA side branches at the level of the first intercostal space appearing in two of the five angiograms (Fig 5). The hemodynamic data as obtained from the nonused IMA have been reported previously [11].

Comment

In the IMAs of all preoperative patients and all control individuals we documented a triphasic Doppler waveform with a high blood flow velocity during systole followed by a much smaller or absent diastolic component. There was a considerable physiologic spread in IMA blood flow velocity among the various individuals. This spread is caused only to a minimal extent by dependency on the insonation angle, because it was maintained rather constant in all measurements. We did not correct for the slight variations in insonation angle because their signif-

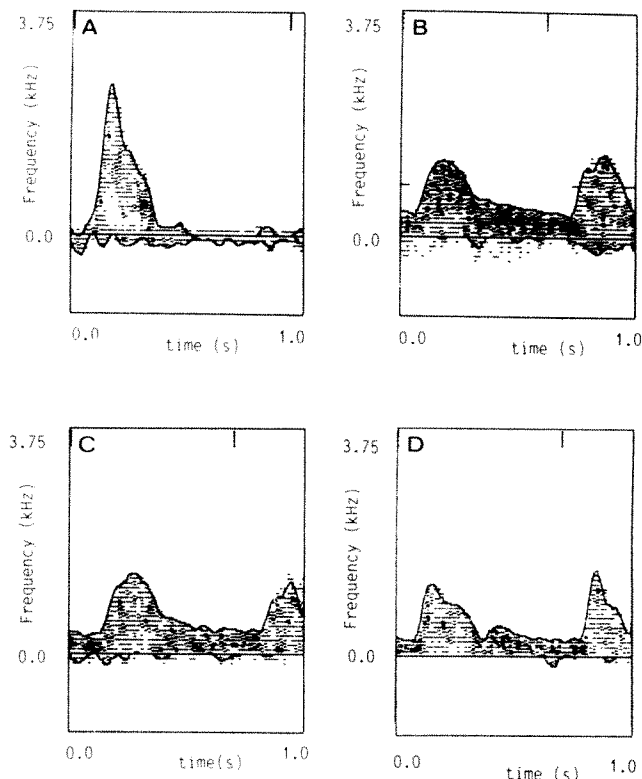


Fig 3. Typical Doppler spectra as obtained from the proximal left internal mammary artery in a patient who underwent myocardial revascularization with use of this conduit: (A) preoperative situation, (B) first postoperative week, (C) 2 months postoperatively, and (D) 6 months postoperatively. Mark at top indicates beginning of systole.

icance is far exceeded by the physiologic spread in IMA blood flow velocity among the various individuals. There was no significant difference in IMA hemodynamics and

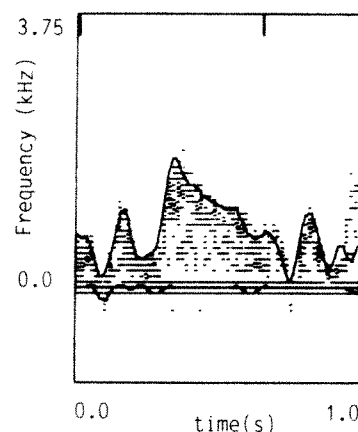


Fig 4. Doppler spectrum from the internal mammary artery conduit as observed in a patient in whom 2 months earlier the internal mammary artery had been anastomosed to the left anterior descending artery. Note the early systolic peak, followed by approximation of the blood flow velocity to zero and the subsequent high diastolic blood flow velocity that exceeds the systolic blood flow velocity. Mark at top indicates beginning of systole.

Table 2. Doppler Spectrum Parameters and Luminal Diameter as Measured in the Internal Mammary Artery Conduit in 14 Patients^a

Parameter	Preop (a)	p Value (a versus b)	1 week Postop (b)	2 Months Postop (c)	p Value (a versus c)	p Value (c versus d)	6 Months Postop (d)	p Value (a versus d)
F _{max} (Hz)	1,943 ± 432	<0.05	1,385 ± 399	1,449 ± 497	<0.05	NS	1,277 ± 255	<0.05
F _{dia} (Hz)	104 ± 109	<0.05	451 ± 148	522 ± 244	<0.05	<0.05	276 ± 199	<0.05
Adv (Hz)	432 ± 96	<0.05	758 ± 210	805 ± 317	<0.05	<0.05	556 ± 144	<0.05
RI	0.94 ± 0.07	<0.05	0.66 ± 0.13	0.64 ± 0.13	<0.05	<0.05	0.78 ± 0.15	<0.05
PI	4.7 ± 1.5	<0.05	1.3 ± 0.4	1.2 ± 0.5	<0.05	<0.05	2.0 ± 0.7	<0.05
Diameter (mm)	3.3 ± 0.3							

^a Values are shown as mean ± standard deviation.

Adv = mean frequency of curve; F_{dia} = end-diastolic frequency of advancing curve; F_{max} = maximum frequency of advancing curve; NS = not significant; PI = pulsatility index; RI = resistance index.

IMA luminal diameter among both control groups and the preoperative patients. Thus older age did not adversely influence the compliance and the degree of intimal thickening in the IMA. This finding may reflect the fact that the presence of a relatively large number of elastic lamellae in the media of the IMA, combined with a well-formed internal elastic lamina, even at advanced age, protects

against intimal thickening and, secondarily, atherosclerosis of this vessel [19-21].

In all IMAs that were used as a conduit for myocardial revascularization we observed conversion from a triphasic blood flow velocity waveform preoperatively to a unidirectional waveform postoperatively. This profound change in waveform pattern remained rather constant during the first 2 postoperative months and then declined, but remained significant at 6 months postoperatively in comparison with the preoperative situation. The unidirectional waveform pattern is considered to be caused by the low resistance of the coronary arterial bed, resulting in a marked increase of diastolic flow through the IMA conduit. In addition, in analogy to the postoperatively observed temporary increase in diastolic flow in the nonused IMA [11], the diastolic flow in the IMA conduit is temporarily enhanced in the early postoperative stage as a result of reactive hyperemia.

In this study we have demonstrated the clinical applicability of Doppler spectrum analysis in the preoperative assessment of suitability of the IMA as a bypass graft in myocardial revascularization and the potential utility of this technique in the postoperative functional assessment of the IMA conduit. The superficial location of the IMA and its relative freedom from severe atherosclerosis contribute to the fact that the results of echo-Doppler scanning of the IMA are generally excellent. In addition, our study shows that B-mode imaging allows accurate preoperative assessment of the luminal IMA diameter, although this may be limited in case of vessel calcification [22, 23]. Another study has demonstrated that B-mode imaging may identify normal and atherosclerotically diseased vessels as verified by contrast angiography [24]. Accurate postoperative measurement of the luminal IMA diameter with B-mode imaging, however, was possible in only 47% of the patients in this study. This low success rate may be primarily due to the fact that successful postoperative B-mode imaging of the IMA is highly dependent on the postoperative course of the vessel and as such is generally jeopardized if the IMA has been dissected free from the chest wall at the first intercostal space.

Preoperative assessment of suitability of the IMA as a conduit in myocardial revascularization may especially be



Fig 5. Postoperative angiogram of left internal mammary artery anastomosed in a sequential fashion to two marginal branches and the circumflex branch of the left coronary artery. Note side branches at the level of the first intercostal space.

valuable in patients who previously have been subjected to median sternotomy or mediastinal irradiation and in those with generalized atherosclerotic disease, such as may be the case in diabetics [25]. Currently, we almost routinely combine use of Doppler spectrum analysis and B-mode imaging in the preoperative and postoperative hemodynamic assessment of the IMA. Such a study can be performed in 20 to 30 minutes with a learning curve of only 2 to 3 weeks. The interobserver variability of this technique is small as long as the insonation angle is kept constant (60 degrees).

Quantitative velocity waveform analysis provides important physiologic data of bypass graft hemodynamics that are not available in pressure or volume flow measurements. The configuration and magnitude of the graft velocity waveform are a function of driving pressure, wall compliance, luminal diameter, and outflow resistance of the coronary arterial bed and of any side branches of the in situ arterial graft [8]. From other studies that applied intraoperative Doppler spectrum analysis in myocardial revascularization procedures, it is known that the graft flow pattern varies with the type and number of outflow coronary arteries [7, 8]. In grafts to the left coronary artery the blood flow velocity is highest in mid-diastole with flow approximating zero in early systole, followed by antegrade flow at end-systole [8, 10, 26, 27]. Grafts to the right coronary artery, however, show forward flow throughout the pulse cycle reflecting the lower right ventricular compressive forces during systole [26]. Recognition of normal systolic and diastolic flow patterns in bypass grafts, in the absence of technical error, may be used to evaluate the effects of revascularization on myocardial contractility. Abnormal flow patterns, such as predominantly systolic flow in a bypass graft to the left ventricle, may indicate diminished local left ventricular contractility [26].

Analogous to intraoperative Doppler spectrum analysis of the IMA conduit, postoperative application of this technique may also detect abnormal flow patterns. Postoperative Doppler spectrum analysis has the ability to detect poor IMA graft function, as evidenced by low to absent diastolic flow velocity, as other investigators have demonstrated intraoperatively [8] and as we have observed postoperatively in serial studies in a few patients who were not incorporated in this study. Such ultrasonic findings may warrant subsequent performance of IMA angiography to detect potential anatomic causes of poor graft function. A number of factors, however, may limit the usefulness of postoperative Doppler spectrum analysis as performed in this study. First, because all postoperative Doppler spectra in this study were obtained from the proximal segment of the IMA, the recorded spectra show a predominantly systolic waveform. In contrast, intraoperative Doppler spectrum analysis of the IMA at the mid or distal conduit level, as performed by us [10], showed a predominantly diastolic pattern. Therefore, in applying postoperative Doppler spectrum analysis as done in this study, any abnormal myocardial contractility, indicative of myocardial damage, may be incorporated in the predominantly systolic waveform. Second, flow sig-

nals resulting from flow distal to residual IMA branches may obscure recognition of flow disturbances resulting from more distal IMA or coronary pathology. Third, the expression of the systolic component as encountered in the proximal IMA conduit may vary with the length of the IMA conduit between the measuring site and the IMA-coronary artery anastomosis.

In summary, preoperative transthoracic B-mode imaging and Doppler spectrum analysis of the IMA are promising techniques in the preoperative morphologic and functional assessment of this vessel. Doppler spectrum analysis may also be used in the postoperative serial assessment of IMA graft function. Postoperatively, in the normally functioning IMA conduit, a lasting significant increase in the diastolic blood flow velocity and decrease in the systolic blood flow velocity are observed, secondary to anastomosis of the IMA to the low-resistance coronary arterial bed.

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Role of Autogenous Tissue Factors in Hemolysis During Cardiopulmonary Bypass Operations

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Pericardial fluid has been implicated as a causative factor in hemolysis during cardiopulmonary bypass operations. Preoperative blood samples were obtained from 10 patients undergoing coronary artery bypass grafting for ischemic myocardial disease. Whole blood samples were separately incubated with autogenous pericardial fluid, pericardium, pleura, vein, skeletal muscle, and fat harvested during the operative intervention. The plasma fraction was separated by centrifugation and assayed for serum free hemoglobin. Statistical analysis was accomplished by the Bonferroni technique to adjust for multiple comparisons. Pericardial fluid-induced hemolysis

was least (20.7 mg/dL). Pleura and muscle contributed significantly to the serum free hemoglobin level (56.3 and 112.3 mg/dL, respectively; $p < 0.05$). Pericardium, vein, and fat did not cause significant elevations of the serum free hemoglobin level. Postbypass hemolysis is an important management consideration that may be minimized by delicate tissue manipulation and attention to minimizing tissue trauma. Avoidance of aspiration of pericardial fluid into the autotransfusion system is not supported.

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Blood transfusion requirements during cardiovascular surgical interventions have decreased with use of blood scavenging apparatus and autotransfusion [1, 2]. Hemolysis after cardiopulmonary bypass-supported operations has been variously attributed to direct mechanical trauma from the scavenging apparatus or the bypass circuit. An early report by Morris and associates [3] suggested that mechanical trauma to the red blood cell may play a minor role in hemolysis and, instead, that the major determinant of corpuscle destruction was contact with pericardial and pleural surfaces. This study is quoted as a rationale, in some institutions, for avoiding aspiration of pericardial or pleural fluid collections into the cell scavenging apparatus used during cardiopulmonary bypass operations. We present our experience and review the tendency of various solid and fluid tissues to cause destruction of red corpuscle membranes, as evidenced by liberation of serum free hemoglobin.

Material and Methods

Adult patients scheduled for elective coronary artery bypass grafting in management of myocardial ischemic disease were studied. After anesthetic induction, 15 mL of arterial blood was drawn from each patient and placed in standard hematological tubes containing EDTA. Pericardial fluid was sampled by aspiration immediately before the pericardium was opened to minimize blood contamination of the fluid. Pericardium, pleura, and subcutaneous fat were harvested before bypass grafting. Skeletal

muscle was harvested from the distal portion of the mammary artery pedicle. Vein was harvested with saphenous vein grafts from the lower leg. One-half gram samples of each tissue type (solid and fluid) were separately incubated in the tubes containing EDTA and whole blood at 37°C for 30 minutes with gentle agitation. Whole blood in EDTA served as the study control. Whole blood hemolyzed in a 1:1 mixture with distilled water served as the indicator of maximal expected hemolysis. After incubation, samples were centrifuged at 2,500 rpm for 15 minutes on an Eppendorff No 5415 centrifuge, and the supernatant was decanted. The supernatant was assayed for serum free hemoglobin on a Perkin Elmer Lambda 4C UV/VIS ultraviolet spectrophotometer at 380 nm, 415 nm, and 450 nm. Serum free hemoglobin content in milligrams per deciliter was calculated as $83.6 [(2 \times A_{415 \text{ nm}}) - A_{380 \text{ nm}} - A_{450 \text{ nm}}]$, where 83.6 = constant of absorption of 1 L of oxyhemoglobin and A = absorbance [4].

Informed consent was obtained from all subjects before study. The study protocol, informed consent, and tissue processing were accomplished in strict accordance with, and the approval of (Jan 1991), guidelines established by the Institutional Review Committee and Department of Defense regulations. Statistical comparisons were accomplished with Bonferroni's technique to adjust for multiple comparisons.

Results

Ten patients (7 male, 3 female) aged 52 to 70 years (mean, 62 years) undergoing elective coronary artery bypass grafting were studied. The operative approach was through a median sternotomy, and grafting was accomplished with mammary artery and saphenous vein grafts. All interventions were uncomplicated.

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Table 1. Serum Free Hemoglobin Concentrations by Site

Site	Mean (mg/dL)	Standard Deviation (mg/dL)	Median (mg/dL)	Range (mg/dL)	Comparison With Plasma Control ^a
Muscle	112.3	174.3	48.5	12.5-586.8	$p < 0.05$
Pericardium	39.6	42.1	26.3	5.9-148.0	NS
Pericardial fluid	20.7	35.8	9.2	4.2-121.2	NS
Pleura	56.3	62.8	25.1	10.9-174.7	$p < 0.05$
Vein	28.0	17.0	26.4	8.4-61.9	NS
Fat	35.8	16.0	31.4	15.9-71.9	NS
Hemolyzed RBC	5,076	1,728	5,213	2,316-8,912	$p < 0.05$
Plasma control	15.1	16.0	9.9	2.5-54.3	NS

^a Comparison of median concentration at each site with plasma control group, using the Bonferroni method of adjusting for comparisons.

NS = not significant; RBC = red blood cells.

Hemolysis was demonstrated with each of the tissues studied. Hemolysis with pericardium, pericardial fluid, vein, and fat was not statistically significantly different than controls (Tables 1, 2). Pleura ($p < 0.05$) and skeletal muscle ($p < 0.05$) incubations demonstrated statistically significant elevations in serum free hemoglobin. Table 1 provides a summary of hemoglobin concentrations for each group and a comparison of the median concentration with that of the control group. Table 2 shows the 95% confidence interval of the median difference of each group from the plasma (control) group.

Comment

Pericardial fluid is an ultrafiltrate of plasma with similar electrolyte concentrations but only one-third the protein concentration. Free fluid within the pericardium is secreted by the visceral pericardium and reabsorbed by the lymphatics of the parietal pericardium; it is found at relatively constant volumes of less than 50 mL. It is our subjective interpretation that some cardiovascular surgeons do not aspirate pericardial or pleural fluids into autotransfusion scavenging systems for fear of causing hemolysis. The argument that pericardial fluid causes hemolysis stems from an early report by Morris and associates [3] that suggested that direct trauma to the red corpuscle may cause some disruption, but that indetermi-

nate properties of pericardial fluid were the major determinants of hemolysis. The report was based on indirect clinical observations that perfused patients' serum free hemoglobin concentrations were higher off bypass when compared with levels measured immediately before the discontinuation of extracorporeal support. Blood scavenged from the pleural and pericardial cavities immediately before coming off bypass was implicated. Laboratory evaluation of the blood in the pleural and pericardial cavities showed evidence of significant hemolysis (pericardial cavity more than pleural). Morris and associates' report was supported by subsequent authors. Siderys and colleagues [5] compared membrane and bubble oxygenation in cardiopulmonary bypass patients and additionally addressed the question of the role of blood contact with the pericardium in producing hemolysis. They developed a method of specifically aspirating the pericardial and pleural cavities of their contained blood, centrifuged the blood cells from the plasma, decanted the plasma, and returned the cell mass to the bypass circuit. Pericardial blood was found to have a serum free hemoglobin concentration of 485 mg/dL, whereas the intracardiac sump and pump blood showed 17 mg/dL and 15 mg/dL, respectively ($n = 6$ patients). Nuclide tagged cells from the pericardial and pleural fluids showed a normal postoperative life span.

Previous authors based their comments on indirect observations and did not discuss specific properties of local tissues (pleura, pericardium, muscle, fat) that may contribute to hemolysis by unavoidable direct contact with blood during surgical procedures. Our study was designed to establish if indeed pericardial fluid causes hemolysis and, additionally, if other autogenous local tissues may be implicated as playing a more important role in red cell destruction.

We were unable to demonstrate statistically significant hemolysis by incubating fresh whole blood and pericardial fluid. In fact, in 6 of 10 patients the serum free hemoglobin concentration of pericardial fluid incubations was less than that of controls. Hemolysis within incubated specimens of pericardium, vein, and fat were higher than controls but did not achieve statistical signif-

Table 2. Ninety-five Percent Confidence Intervals of Median Difference Between Serum Free Hemoglobin Concentrations of Each Site and Control Group

Site	95% Confidence Interval (mg/dL)
Muscle	3.6-341.4
Pericardium	-4.3-82.8
Pericardial fluid	-23.8-55.2
Pleura	2.5-123.7
Vein	-2.5-37.2
Fat	-5.4-42.7
Hemolyzed RBC	3,237-7,156

RBC = red blood cells.

icance. These are tissues that are subjected to comparatively less traumatic dissection than pleura or skeletal muscle encountered during mammary artery mobilization. The levels of hemolysis in muscle and pleura incubations did achieve statistical significance. Clinically, we suggest that minimal and gentle handling of pleura and muscle during dissection of the mammary artery pedicle may reduce liberation of tissue factors responsible for hemolysis. We do not suggest that blood collected within the pleura should be discarded, as current blood salvage technology includes cell washing systems that may remove hemolytic tissue factors.

Hemolysis often accompanies clostridial infections [6]. Clostridia-associated hemolysis results from lysolecithin activity [7]. Lysolecithins are a release product of damaged cell membranes that may also be responsible for red cell disruption after surgical procedures. Lysolecithins are naturally occurring hydrolytic products of phospholipase A₂ that are found within cell membranes and function as modulators of membrane biologic functions. These products are usually found in low concentrations in the serum. When released from damaged membranes they are quickly deactivated by binding to serum albumin and phospholipase B₂. When unbound serum lysolecithins contact the red corpuscle membrane they enter the membrane and act as a detergent to remove membrane lipids and also activate complement. These activities create openings within the corpuscle membrane large enough to allow electrolyte and fluid influx. The resultant solute flow causes an osmotic hemolysis [8].

The pleura generally does not undergo extensive dis-

section. We are unable to conjecture as to a property of pleural tissue that may be responsible for hemolysis. The patient undergoing cardiac revascularization is subject to dissection of numerous types of tissue and cardiopulmonary bypass, both of which may play a more prominent role than pericardial fluid in postoperative hemolysis.

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Preimplantation Alteration of Adenine Nucleotides in Cryopreserved Heart Valves

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To assess the initial metabolic phase of cellular injury from cardiac valve processing, high-energy phosphate concentrations were analyzed in valve leaflets subsequent to critical processing steps. Using a porcine model, valves were processed in a manner identical to human homografts, with 58 randomly assigned to five groups representing distinct preparation phases. Group I (controls) sustained 40 minutes of warm ischemia concluded by liquid nitrogen immersion. Remaining groups similarly endured 40 minutes of ischemia, but were subsequently prepared according to stepwise design: II, warm ischemia + 24 hours of 4°C ischemia; III, warm ischemia + 24 hours of 4°C antibiotic disinfection; IV, warm ischemia + 24 hours at 4°C (without antibiotics) + cryopreservation (–1°C/min cryoprotected freezing); and

V, warm ischemia + disinfection + cryopreservation. At each regimen's conclusion leaflet extracts were assayed by high-performance liquid chromatography for high-energy adenine nucleotides (adenosine triphosphate, adenosine diphosphate, adenosine monophosphate) and catabolites. A 47% and 86% decrease in cellular adenosine triphosphate level was observed in group III and group V leaflets, respectively. The level of total adenine nucleotides was maintained up to cryopreservation; thereafter a 74% decrease was noted. Catabolite analysis confirmed incomplete degradation of adenine nucleotides indicating cellular metabolic resilience throughout standard homograft preparation in valves previously exposed to 40 minutes of warm ischemia.

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Congenital and acquired cardiac valvular pathology continues as a prevalent clinical problem, often requiring prosthetic replacement. Because of the morbidity associated with the conferred "prosthetic valve disease," transplanted human valves are under increasing scrutiny as they have demonstrated certain specific advantages over xenograft and mechanical replacement heart valves [1]. With increased utilization, those factors potentially influencing prolonged valve durability, the major controversial issue, remain incompletely characterized. It has been proposed by some that such determinants may be related to the postimplantation cellular integrity of homograft leaflet fibroblasts [2–4].

Since the initial homograft aortic valve replacements by Ross and Barratt-Boyes in 1962 [5, 6], many methods have been employed for preparation before storage of such tissue. Historically, these have included various methods of chemical disinfection and sterilization including high-concentration antibiotics, β -propiolactone, ethylene ox-

ide, irradiation, and glutaraldehyde treatment. Most have been demonstrated to damage the tissue and thereby negatively influence long-term homograft durability [7–9]. Conversely, less rigorous techniques such as maintenance in culture medium (4°C) for up to 6 weeks have provided satisfactory results [10–12]. At present, however, the majority of harvested human valves are disinfected using antibiotic formulations having low toxicity and preserved by controlled-rate freezing (–1°C/min) with 10% dimethylsulfoxide as a cryoprotectant [13, 14].

Cryopreservation is a well-defined and reproducible technique [15], but other "preimplantation processing" steps occurring between valve harvest and implantation are less uniform. Details of one effective method include a rinsing of the procured valve in saline solution and storage in cold (4°C) nutrient medium for 24 hours, during which transport to processing facilities and antibiotic disinfection are usually accomplished. Valves are then cryopreserved as described and maintained in vapor phase liquid nitrogen until the time of transplantation, when they are thawed by means of a dilutional warming procedure in the operating room. Each step between donor death and implantation retains a potential for homograft alteration through injury to the cellular and matrix components. Morphologic criteria and in vitro cell viability assays have been used as a means of monitoring the effects of processing on the valvular tissue [3]; we were interested in quantitating high-energy phosphate

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concentrations as a function of the various processing steps. Intracellular concentration changes of adenine nucleotides essential for anabolic cellular function may serve as an estimate of the metabolic status of the cell. This type of metabolic assay of high-energy phosphate measures ischemic injury presumably during a prelethal injury phase. This may function as an initial measurement of ischemic stress, rather than using a less sensitive indicator of frank cell death. The purpose of this experiment was to accurately measure these phosphorylated adenine nucleotides and their products of catabolism, thereby evaluating the extent of such injury occurring consequent to cold ischemia, antibiotic disinfection, and cryopreservation.

Material and Methods

Animal Preparation

Fifty-eight semilunar cardiac valves were obtained from 9-month-old female Yorkshire and Poland China swine after a 40-minute period of corporeal warm ischemia between death of the animal and cardiectomy at the slaughterhouse. Aortic and pulmonary valve conduits were dissected, roots opened between adjacent cusps, and the leaflets subjected to vigorous scraping with a rubber policeman to remove endothelium. Random scanning electron microscopy was performed to verify endothelium removal. The excised leaflets were either stored in liquid nitrogen (-190°C) or refrigerated (4°C) as defined by the experimental protocol.

Experimental Groups

Group I ($n = 12$) leaflets were immediately immersed in liquid nitrogen after harvest (ie, control; 40-minute warm ischemic time) to establish baseline adenine nucleotide concentrations. Group II ($n = 12$) leaflets were placed in serum-free RPMI 1640 nutrient medium (Gibco Co, Grand Island, NY) at 4°C for 24 hours (cold ischemic time; analogous to cold transport of donor tissue to processing centers, but in the absence of antibiotics by design) followed by rapid freezing by immersion in liquid nitrogen. Group III ($n = 11$) leaflets were subjected to 4°C antibiotic disinfection (cold disinfection time, virtually analogous to clinical protocol) followed by immersion in liquid nitrogen. The antibiotic formulation consisted of a serum-free RPMI 1640 nutrient media solution containing cefoxitin, $240\text{ }\mu\text{g/mL}$; lincomycin, $120\text{ }\mu\text{g/mL}$; polymyxin B sulfate, $100\text{ }\mu\text{g/mL}$; and vancomycin, $50\text{ }\mu\text{g/mL}$ [15]. Group IV ($n = 12$) was subjected to cold ischemia (identical to group II valves, 24 hours at 4°C , in antibiotic-free media) but then cryopreserved as follows: 10% each of dimethylsulfoxide and fetal calf serum in RPMI 1640, frozen at a rate of $-1^{\circ}\text{C}/\text{min}$ to -60°C (CryoMed 1010 Micro computer), and stored in vapor phase liquid nitrogen (-190°C) (CryoMed freezer model CMS-450A, New Baltimore, MI) [15]. Group V ($n = 11$) leaflets were subjected to all of the processing steps, modeling a completed homograft preparation with brief warm ischemia (ie, 40 minutes of warm ischemia, 24 hours of cold antibiotic disinfection, and cryopreservation). Leaflets were thawed in single-valve trileaflet sets, and one cusp

was randomly selected for analysis of all adenine nucleotide metabolites by high-performance liquid chromatography.

Extraction Procedure

Using cold (4°C) instruments to manipulate the tissue, the selected leaflet from each valve was homogenized by hand for 30 minutes at 10°C in 12% trichloroacetic acid solution. The mixture was separated by centrifugation (10 minutes, 3,000 rpm) and the soluble extract removed and neutralized using a tri-*n*-octylamine:freon (1:2) mixture. After vortexing, the organic phase was separated by centrifugation (10 minutes, 3,000 rpm) and stored in 1.5-mL polypropylene microcentrifuge tubes (Baxter, McGaw Park, IL) at -70°C . The postextraction pellets of denatured leaflet protein were dissolved in 0.6 N sodium hydroxide for protein determination according to the method described by Lowry and associates [16] (Gilford Response UV-VIS spectrophotometer [Oberlin, OH] at 725 nm).

High-Performance Liquid Chromatography Analysis

Aliquots ($80\text{ }\mu\text{L}$) were loaded onto a Waters Intelligent Sampler Processor model 710B high-performance liquid chromatography column (Waters Associates, Milford, MA). A solvent delivery system model 6000A (Waters Associates) along with a solvent selector model 101 (Alltech Associates, Deerfield, IL) was used. Step gradient separation of the adenine pool metabolites (adenosine triphosphate [ATP], adenosine diphosphate [ADP], adenosine monophosphate [AMP], oxidized form of nicotinamide adenine dinucleotide [NAD^+], adenosine, inosine, hypoxanthine, and xanthine) was achieved using a NOVA-Pak-A (C18; $5\text{-}\mu\text{m}$ particle size; $10 \times 8\text{ mm}$) chromatographic column inside a radial compressor module model RCM 100 (Waters Associates) (Fig 1). Ammonium phosphate (100 mmol/L ; pH 5.5) was used to elute ATP, ADP, uric acid, hypoxanthine, and xanthine; NAD^+ was eluted with 7% methanol; and inosine and adenosine were eluted with 40% methanol. The adenine pool metabolites were integrated and quantitated to external standards through a visible/ultraviolet detector model 490 and a data module model 730 (Waters Associates). Retention time, peak area, and amounts of all eluted adenine metabolites were recorded on each chromatogram and normalized to the average concentration of protein in the units of adenine metabolite per milligram of protein $\pm$ standard error of the mean. Chemical reagents and buffers were purchased from Sigma Chemical Company (St. Louis, MO). High-performance liquid chromatography-grade ammonium phosphate and methanol were purchased from Fisher Scientific (Fair Lawn, NJ). Distilled and deionized water was processed through the Milli-Q System Millipore (Bedford, MA).

Statistical Analysis

The statistical analysis program SAS (Statistical Analysis System Institute, Cary, NC) processed on an IBM 386 computer was used to determine statistical significance, where p was less than 0.05 using a one-way analysis of

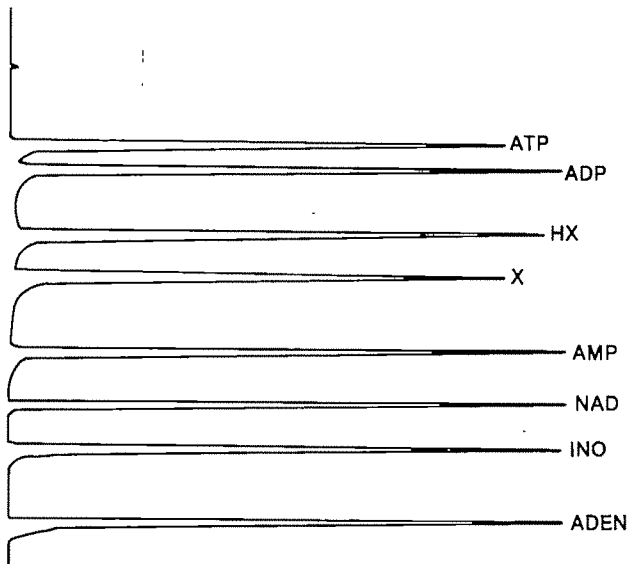


Fig 1. Representative peaks of adenine nucleotide pool metabolites as generated by step-gradient high-performance liquid chromatographic elution. Retention time, peak area, and amounts of each metabolite are recorded from each chromatogram. (ADEN = adenosine; ADP = adenosine diphosphate; AMP = adenosine monophosphate; ATP = adenosine triphosphate; HX = hypoxanthine; INO = inosine; NAD = nicotinamide adenine dinucleotide, oxidized form; X = xanthine.)

variance between all possible combinations of each step of the experimental model. A Scheffé's multiple comparison procedure was used to identify significant differences between treatment groups.

Results

Valve leaflets (excluding endothelium) were analyzed after each processing step of a representative homograft valve cryopreservation protocol to quantify the following metabolites: ATP, total adenine nucleotides (TAN = AMP + ADP + ATP), and total diffusible purines (TDP =

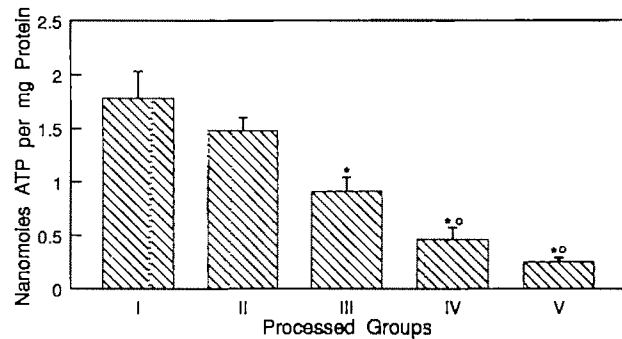


Fig 2. Progressive degradation of adenosine triphosphate (ATP) existing at the completion of each processing phase: (I) warm ischemia, (II) cold transport, (III) antibiotic disinfection, (IV) cryopreservation, and (V) cryopreservation with antibiotics. (* $p < 0.05$ versus group I; ° $p < 0.05$, group IV versus group II and group V versus group III.)

adenosine + inosine + hypoxanthine + xanthine) (Table 1, Figs 2-4).

Group I: 40 Minutes of Warm Ischemia (Control)

After 40 minutes of warm ischemia 12 randomly assayed leaflets contained the following baseline concentrations: ATP = 1.78 ± 0.25 nmol/mg protein, TAN = 2.59 ± 0.33 nmol/mg protein, and TDP = 3.51 ± 0.41 nmol/mg protein (see Figs 2-4). Values for all metabolites are listed in Table 1.

Group II: 40 Minutes of Warm Ischemia + 24 Hours of 4°C Ischemia (No Antibiotics)

A 17% reduction in ATP (see Fig 2) was observed in group II leaflets (1.48 ± 0.12 nmol/mg protein) as compared with group I levels, indicative of some ATP degradation induced by this step. In addition, there was an 8% increase in TAN (2.81 ± 0.34 nmol/mg protein) (see Fig 3) and a 6% increase in TDP (3.75 ± 0.87 nmol/mg protein) (see Fig 4) as compared with group I. This commenced a trend of ATP degradation to lower energy adenine nucleotides

Table 1. Metabolites (nmol/mg protein)^a.

	Group I (WIT only)	Group II (WIT + 24 h 4°C ischemia)	Group III (WIT + 24 h 4°C antibiotic disinfection)	Group IV (WIT + 4°C ischemia + cryopreservation)	Group V (WIT + 4°C disinfection + cryopreservation)
ATP	1.78 ± 0.25	1.48 ± 0.12	0.91 ± 0.13^b	0.46 ± 0.11^b	0.25 ± 0.04^b
ADP	0.59 ± 0.07	0.55 ± 0.05	0.33 ± 0.07	0.27 ± 0.05	0.25 ± 0.03
AMP	0.40 ± 0.10	0.78 ± 0.21	1.00 ± 0.40	0.14 ± 0.07	0.18 ± 0.07
Adenosine	0.18 ± 0.06	1.20 ± 0.29	6.10 ± 3.50	0.52 ± 0.10	3.10 ± 0.70
Inosine	1.50 ± 0.30	0.72 ± 0.20	0.87 ± 0.20	0.50 ± 0.50	0.71 ± 0.13
Hypoxanthine	1.70 ± 0.25	0.78 ± 0.16	0.73 ± 0.24	0.12 ± 0.06	0.07 ± 0.03
Xanthine	0.00 ± 0.00	1.10 ± 0.63	0.10 ± 0.08	0.09 ± 0.08	0.05 ± 0.04
NAD ⁺	0.50 ± 0.04	0.33 ± 0.04	0.29 ± 0.12	0.07 ± 0.04	0.23 ± 0.04

^a Adenine nucleotide metabolite concentrations ($\pm$ standard error of the mean) existing at the completion of each step of preimplantation processing.
^b $p < 0.05$ versus group I by analysis of variance.

ADP = adenosine diphosphate; AMP = adenosine monophosphate; ATP = adenosine triphosphate; NAD⁺ = nicotinamide adenine dinucleotide, oxidized form; WIT = warm ischemia.

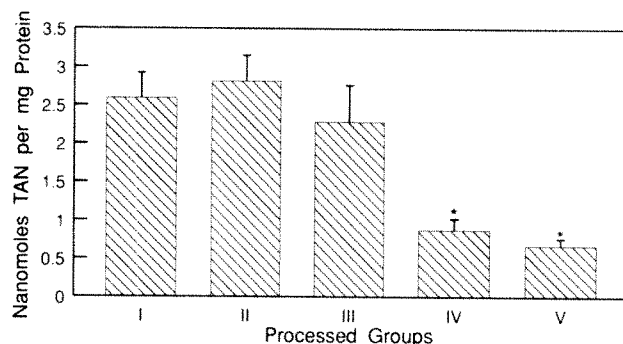


Fig 3. Total adenine nucleotides (TAN) existing at the completion of each processing phase: (I) warm ischemia, (II) cold transport, (III) antibiotic disinfection, (IV) cryopreservation, and (V) cryopreservation with antibiotics. (* $p < 0.05$ versus groups I, II, and III.)

and ultimately to purine byproducts (both TAN and TDP were increased). However, statistical significance was not reached by this group of valves.

Group III: 40 Minutes of Warm Ischemia + 24 Hours of 4°C Ischemia With Antibiotics

Antibiotic disinfection resulted in a 49% reduction (see Fig 2) in ATP with respect to control leaflets (0.91 ± 0.13 nmol/mg protein; $p \leq 0.0001$ versus group I). However, TAN concentrations in group III (2.28 ± 0.48 nmol/mg protein) were not significantly reduced. It should be emphasized that through the completion of the antibiotic step, total high-energy phosphate metabolites (TAN) were statistically maintained at baseline 40-minute levels (see Fig 3), indicating that during these stages ATP degradation proceeds mainly to its lower energy phosphates (ie, ADP and AMP). However, levels of diffusible purines were 55% higher (7.83 ± 1.84 nmol/mg protein) than in group I ($p = 0.0006$) (see Fig 4). This accumulation of byproducts is consistent with degradation of ATP to TAN and partial TAN degradation to adenosine, inosine, hypoxanthine, and xanthine.

Group IV: 40 Minutes of Warm Ischemia + 24 Hours of 4°C Antibiotic-Free Ischemia + Cryopreservation

The consequences of cryopreservation were evaluated in groups IV and V, which differed by the presence or

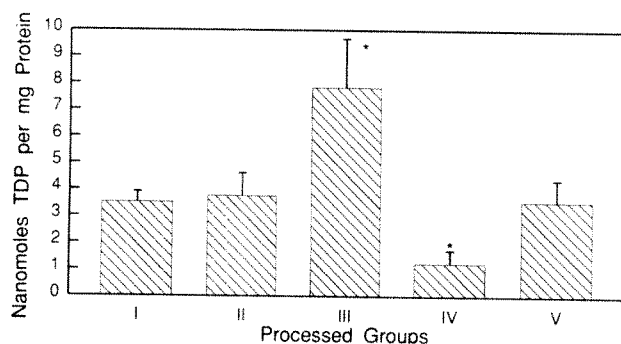


Fig 4. Total diffusible purines (TDP) at the completion of each phase of cardiac valve transplant preparation: (I) warm ischemia, (II) cold transport, (III) antibiotic disinfection, (IV) cryopreservation, and (V) cryopreservation with antibiotics. (* $p < 0.05$ versus groups I, II, and V by analysis of variance.)

absence of antibiotics. In group IV, the valves exposed to cryopreservation without antibiotics, there was a significant depletion of ATP by 74% (0.46 ± 0.11 nmol/mg protein) compared with control ($p \leq 0.0001$) (see Fig 2). The 69% reduction ($p = 0.0001$) in ATP between groups II and IV (see Fig 2) quantitates the effect of cryopreservation and warm and cold ischemia without exposure to antibiotics. Similarly, cryopreservation without antibiotics effected a 66% TAN depletion from baseline (0.87 ± 0.15 nmol/mg protein) (see Fig 3). With the addition of cryopreservation to 24 hours of cold ischemia (group IV), there was a 69% diminution ($p = 0.0001$) in TAN from antibiotic-free cold ischemia levels (group II). There was a significant change in total diffusible purines (1.24 ± 0.49 nmol/mg protein) in group IV ($p < 0.05$ versus baseline).

Group V: 40 Minutes of Warm Ischemia, 24 Hours of 4°C Antibiotic Disinfection, and Cryopreservation (Complete Cryopreservation Protocol)

Analysis of ATP in group V (0.25 ± 0.04 nmol/mg protein) measures the cumulative effects of all steps involved in the preparation of clinical homograft cardiac valves. There was an 86% ($p = 0.0001$) and 83% ($p = 0.0001$) reduction in ATP as compared with baseline (group I) and 24 hours of cold ischemia without antibiotics (group II), respectively (see Fig 2). Cells in leaflets exposed to both antibiotics and cryopreservation demonstrated a 73% reduction in ATP ($p = 0.0001$) versus leaflets experiencing 24 hours of cold ischemia with antibiotics (group III) (see Fig 2).

The effect of all steps (group V) on TAN levels (0.68 ± 0.09 nmol/mg protein) was similar to that seen with group IV. Concentrations of AMP, ADP, and ATP in the fully processed leaflets demonstrated a 74% ($p = 0.0001$) reduction as compared with group I (see Fig 3).

The total diffusible purine concentration in fully processed leaflets (3.56 ± 0.82 nmol/mg protein) was 55% less than the purine level in leaflets assayed after antibiotic disinfection alone (see Fig 4). The NAD^+ levels remained essentially unchanged (0.49 ± 0.06 nmol/mg protein) until the cryopreservation steps, which resulted in a slight reduction.

Comment

This study of porcine cardiac valves was designed to mimic favorable harvest conditions in which the warm ischemic time was limited to 40 minutes, correlating with a brief period between cessation of donor heartbeat and procurement, such as might occur in a multiple organ harvest setting. Experimental tissue exposed to this degree of ischemia conveniently served as control groups with which to compare metabolite levels after later pre-implantation processing steps. Twenty-four hours of cold ischemia did not cause reductions in total high-energy phosphate concentrations from baseline (see Fig 3). However, 24 hours of cold ischemia resulted in a decrease in the ATP level that, although not statistically significant, was subsequently observed throughout processing. This finding indicates that although the ATP level is diminished at this stage, the majority of degradation occurs

only through to ADP and AMP (reflected in total adenine nucleotide concentrations; confirmed by the measured increases in ADP and AMP) due to incomplete breakdown of ATP or partial restoration by alternate pathways. The purpose of this particular experimental grouping, however, was to differentiate the cold ischemic effects alone (group II) from cold ischemia combined with disinfection (group III).

Antibiotics and Processing-Associated Injury

Many aggressive antibiotic regimens that include antifungal and high-dose antibiotic mixtures have been detrimental to fibroblast viability [17], but antibiotic combinations similar to the one employed in this study appear relatively benign as demonstrated by tissue culture and proline uptake assessment [18-20]. Independent of antibiotic toxicity [21, 22], this study has substantiated that metabolic depletion is, in fact, occurring during 24 hours of cold ischemia and antibiotic disinfection. However, in this study the majority of ATP degradation occurring during antibiotic disinfection generates only to ADP and AMP, which is noteworthy considering that it is the conservation of total high-energy phosphates (not ATP alone) that is critical to a cell's ability to maintain basal function and integrity [23]. Such changes are potentially reversible (eg, conversion of ADP and AMP to ATP) and appear to be likely due to the ischemia associated with the time necessary for disinfection rather than chemical injury. The effect of disinfection disappears when comparing cryopreservation with and without antibiotics, because cryopreservation after disinfection results in an additional 46% depletion of ATP. Regardless of whether prior antibiotic disinfection treatment is used, apparently the cryopreservation phase is responsible for the largest decrease in ATP. This information can be used to develop disinfection strategies that may be even less metabolically costly. Total avoidance of antibiotic disinfection with the subsequent enhanced risk for transmission of infectious disease to the recipient does not appear to be worth the minimal "gain" of reduced metabolic cellular leaflet injury and its theoretical effect on long-term performance.

DMSO Cryopreservation and Cellular Metabolic Injury

With subsequent cryopreservation, significant reductions in high-energy phosphates were observed. Cryopreservation alone, subsequent to only warm ischemia and 24 hours of 4°C ischemia without antibiotics, was responsible for a substantial depletion of ATP (74%) (see Fig 2), which was greater than that imparted by cold ischemia (17%) or cold disinfection (47%). The effects of all preprocessing steps were synergistic in the diminution of adenine nucleotides. Nevertheless, leaflet cells still retained measurable amounts of high-energy phosphates after all of the processing steps (see Fig 3).

Metabolic Depletion, Cell Injury, Viability, and Durability

Determination of the relationship between valvular leaflet fibroblast viability and the long-term function and durability of homografts has been the focus of a few investi-

gations and numerous postulations [17, 24, 25]. Before this interesting question can be addressed, the initial response of the leaflet fibroblast cell population to ischemia and subsequent processing steps must be defined. Adenine nucleotide quantitation is not by itself a viability assay; however, it is a specific indicator of the overall metabolic state of the leaflet fibroblast cell population. Our data define a progressive diminution of high-energy phosphate with each step of preimplantation processing. It is reasonable to assume that as these nucleotides are increasingly depleted, a percentage (without attempting to assign a value) of fibroblasts will lose their ability to structurally maintain cell membranes, thus leading to irreversible injury. It is possible that only after relatively complete depletion of high-energy phosphates in the cell population (which this study did not find, even in the fully processed groups) will irreversible metabolic injury be manifest in the majority of fibroblasts. Unlike specific morphological assays [26], which examine irrefutable structural criteria for injury or death of fibroblasts, the aim of this investigation was to delineate the energy reserve of the leaflet fibroblast population. Few studies have carefully analyzed the early injury response (before irreversible cell injury), a period when such insults may be reversible and responsive to technical modifications, thereby potentially mitigating later effects on ultimate viability. Such changes in high-energy phosphate status might also precede reductions in energy-dependent cell functions such as proliferation, protein transport, and synthetic activity [19].

The hypothesis that cellular viability is a critical determinant of long-term clinical performance rests on the notion that it is the extent of cellular viability *at the time of implantation* that is the key issue [4]. If harvesting and processing protocols are to be designed to maximize cellular viability, then studies like this one are fundamental to understanding the effects of preimplantation processing on heart valve tissue [26-28]. An alternative concept might be that it is the extent of functional viability (ie, fibroblast capable of proliferation and structural protein synthesis) some weeks or months after transplantation that is critical to enhancing valve durability. This being the case, processing methods that result in cells that not only "appear" viable but that have significant metabolic reserve with which to weather the peritransplantation stress could lead to better leaflet fibroblast functional recovery.

High-Performance Liquid Chromatography

High-performance liquid chromatography assays have been employed to quantitate adenine nucleotide concentrations in myocardial cells after ischemia and reperfusion injury [29]. This study demonstrates the feasibility of this method for detecting nanomolar concentrations of the adenine nucleotide metabolites in cardiac valvular leaflets as well. Other methods for adenine nucleotide determination include enzymatic analysis and nuclear magnetic resonance; however, the former depends on generation or consumption of a substrate in subcellular reactions, whereas the latter requires fairly large samples [30, 31].

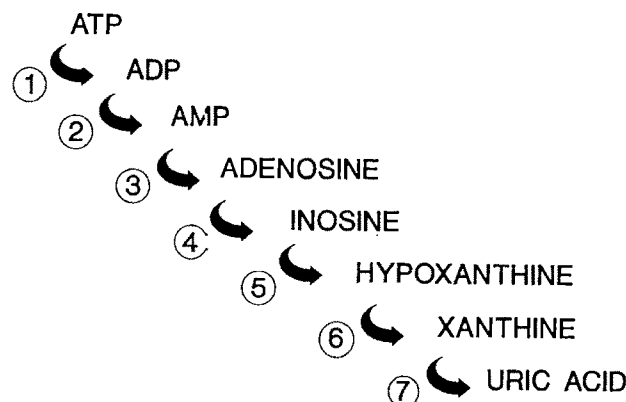


Fig 5. Degradation of adenosine triphosphate (ATP) to its lower energy metabolites and constitutive purine bases. Circled numbers indicated principal enzymes responsible for ATP catabolism: 1 = ATP kinases, 2 = adenylate kinase, 3 = cytosol 5'-nucleotidase, 4 = adenosine deaminase, 5 = purine nucleoside phosphorylase, 6 = xanthine oxidase, 7 = xanthine oxidase. (ADP = adenosine diphosphate; AMP = adenosine monophosphate.)

The progression of biochemical changes in the leaflet fibroblasts has been examined with proton (^1H) and phosphorous (^{31}P) magnetic resonance spectroscopy, and demonstrated a time-dependent depletion of ATP stores reflected by an increase in inorganic phosphate; after 2 hours of harvest-related ischemia, increases in lactate concentration were measured by the nuclear magnetic resonance technique indicating the onset of anaerobic metabolism [30]. These data are quite consistent with our high-performance liquid chromatography results.

An advantage of the high-performance liquid chromatography technique resides in its utility for analysis of the entire high-energy phosphate pool in a "snapshot" fashion throughout the degradatory cascade [32] (Fig 5). All catabolism reactions up to and including the production of adenosine are completely reversible and allow for the possibility of adenosine phosphorylation into a high-energy metabolite and reutilization. Conversely, the freely diffusible purine inosine cannot be converted to adenosine because mammalian cells do not contain appreciable amounts of the necessary inosine kinase [31]. Phosphorylated moieties are restricted to the intracellular milieu.

The remaining components of the adenine nucleotide pool, the diffusible purine bases adenosine, inosine, hypoxanthine, and xanthine, were quantitatively assessed in this study to confirm the high-energy phosphate degradation seen. As total high-energy phosphates are depleted, there should be a concomitant increase in total purine concentrations. This phenomenon was observed through the antibiotic phase in our study. Compared with baseline purine levels, leaflets exposed only to cold ischemia versus those subjected to cold ischemia plus antibiotic disinfection experienced a 6% and 55% increase in purine levels, respectively (see Fig 4). Thus, the greatest increase in TDP was experienced by those groups with the longest decrease in high-energy phosphates. This confirms a certain portion of the TAN pool is in fact proceed-

ing to various metabolites on the lower end of the degradatory pathway (see Fig 5). It must be noted, however, that this linear increase in TDP was blunted at the cryopreservation step. The dilutional liquid media technique for removal of dimethylsulfoxide during thaw may be responsible for a "wash out" of these bases as seen in groups IV and V. Furthermore, the mandatory immersion during disinfection may also account for the lower TDP levels found in both nonantibiotic and antibiotic-treated cryopreserved leaflets.

Time- and Process-Dependent Depletion of High-Energy Adenine Nucleotides

The ATP and TAN concentrations measured at the completion of each step of the cryopreservation process indicate progressive metabolic insult to the valvular leaflet cells. This injury becomes quantitatively important at the antibiotic disinfection step when considering only ATP, whereas TAN depletion does not become significant until later, after cryopreservation. These methods analyze and characterize metabolic effects, which are potentially reversible and thus may be useful in monitoring technological modifications in homograft processing.

These detailed biochemical studies suggest that cardiac valvular leaflet fibroblasts are remarkably metabolically resilient and withstand significant perturbation of energy metabolism during processing. The cell population demonstrates measurable energy reserve when the obligatory processing stages are preceded by relatively short harvest-associated warm ischemia (40 minutes) [33]. The observed metabolic response to the summation of ischemia, antibiotic disinfection, and cryopreservation suggests that these leaflet matrix cells retain reduced but not exhausted intracellular high-energy adenine nucleotide stores. Therefore, at the time of implantation, the population of matrix leaflet cells within the homograft cusps, although significantly altered, are not completely metabolically exhausted by the processing steps inherent in current cryopreservation methods.

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Interstitial pH During Myocardial Preservation: Assessment of Five Methods of Myocardial Preservation

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We investigated changes in myocardial pH during cardioplegic arrest with five methods of preservation at 15° ± 1°C. Twenty-five dogs were subjected to cardiopulmonary bypass for 150 minutes. Group I (control) had hypothermia only. Group II received THAM-buffered blood cardioplegia, group III a bicarbonate-buffered blood cardioplegic solution, group IV infusions of hyperkalemic blood, and group V oxygenated St. Thomas 2 solution. After 120 minutes of ischemia, interstitial pH in group I was markedly depressed (6.4 ± 0.07 ; $p < 0.01$). The pH in groups II and IV was well maintained (7.23 ± 0.05 and 7.27 ± 0.07) and differed significantly ($p < 0.05$) from that of the remaining groups. The pH in groups III and V was less well maintained (7.14 ± 0.02 and 7.01 ± 0.05), with no significant difference ($p > 0.05$) between

these two groups. Postreperfusion functional recovery after 45 minutes was $24\% \pm 6\%$ in group I, $92\% \pm 3\%$ in group II, $82\% \pm 5\%$ in group III, $84\% \pm 4\%$ in group IV, and $66\% \pm 6\%$ in group V. Creatine kinase levels were significantly ($p < 0.01$) increased and ultrastructural damage was more prominent in group I compared with the remaining groups. Myocardial water content significantly increased in all groups. We conclude that a strongly buffered blood-based cardioplegic solution is more effective in preventing interstitial acidosis during moderate hypothermia and that maintenance of an optimal tissue pH plays an important role in postischemic functional recovery.

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Myocardial arrest is commonly used as an adjunct in cardiac operations [1]. Since the introduction of elective cardioplegic arrest by Melrose and his colleagues [2] in 1955, different methods and techniques have been advocated for clinical use during cardiac operations [3-7]. The relative efficacy of these methods in achieving optimal protection of the myocardium has been debated in numerous animal and clinical studies [8-11]. Most of these studies have demonstrated the advantages of sanguineous over asanguineous solutions in preserving myocardial metabolism and ultrastructure [12-15]. In contrast, some clinical studies show no difference between sanguineous and asanguineous solutions, leading to an unsettled controversy [16-18].

During myocardial anaerobiosis the production of high-energy phosphates from glycolysis is not sufficient to cover the myocardial energy deficit that develops with progressive duration of ischemia [19]. The decrease in high-energy phosphates is accompanied by the accumulation of hydrogen ions and lactate [20]. The increased intracellular hydrogen ion concentration and the resultant

tissue acidosis finally leads to a self-inhibition of anaerobic glycolysis [21]. Administration of cardioplegic solutions and hypothermic techniques can delay the metabolic consequences of ischemia, but only for a limited time.

In 1975 Bretschneider and his colleagues [22] proposed the buffering of cardioplegic solutions as a method to increase the ischemic tolerance of the myocardium during elective arrest. This proposal was based on the possibility that buffering could facilitate the washout of hydrogen ions and lactate, thus enabling glycolysis to continue. Recent work by Del Nido and associates [23] demonstrated the effectiveness of histidine-buffered and blood-based solutions in maintaining interstitial pH levels close to preischemic levels.

As it is impossible in the clinical setting to monitor the decrease of myocardial energy production continuously or intermittently, the maximum period of arrest believed to be safe for an individual patient is an arbitrary estimate, based on clinical experience and experimental studies.

In the present study, we assessed the influence of five methods of myocardial preservation on myocardial tissue acidosis during induced myocardial ischemia. The five methods were hypothermia, THAM (Tris-hydroxymethyl-aminomethane)-buffered blood cardioplegia, bicarbonate-buffered blood cardioplegia, hyperkalemic blood, and oxygenated St. Thomas 2 crystalloid solution.

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Table 1. Composition of the Cardioplegic Solutions

Component	Group II	Group III	Group IV	Group V
Potassium (mmol/L)	12-14	12-14	12-14	16
Magnesium (mmol/L)	16	16	0.82	16
Calcium (mmol/L)	2	2	1.9	2
NaHCO ₃ (8.5%) (mL)	...	30	...	10
THAM (mmol/L)	0.6	...	...	...
Albumin (20%) (mL)	...	50	...	...
Mannitol (25%) (mL)	40	...	...	...
Procaine (mg)	200	200	...	...
Hemoglobin (g/dL)	4.2 ± 0.32	4.27 ± 0.44	6.05 ± 0.17	0.00
pH	7.6	7.8	7.4	7.8
Osmolality	320	327	297	324

NaHCO₃ = sodium bicarbonate; THAM = Tris hydroxymethyl aminomethane.

Material and Methods

Animals

Twenty-five adult beagle dogs, matched for weight (18 to 22 kg) and age, were obtained from the animal care facilities of the University of the Orange Free State. All animals received humane care in compliance with the "Principles of Laboratory Animal Care" (National Society for Medical Research) and the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH publication No. 85-23, revised 1985).

Cardioplegic Solutions

The formulation of the different cardioplegic solutions is listed in Table 1. Hypothermia alone, at 15° ± 1°C, was used as a control. The THAM-buffered and bicarbonate-buffered cardioplegic solutions were prepared by mixing freshly oxygenated blood from the perfusion circuit with the corresponding crystalloid solutions (1:1). The hyperkalemic blood solution was prepared by adding potassium chloride to freshly oxygenated blood to a concentration of 12 to 14 mmol/L. The St. Thomas 2 solution was made up in the conventional composition [24] and oxygenated with 95% oxygen and 5% carbon dioxide.

Interstitial pH Measurement

Myocardial interstitial pH was measured with a combined hydrogen ion-sensitive miniature glass electrode (Micro-electrodes Inc, Londonderry, NH) housed in the beveled end of a 21-gauge stainless steel needle with an outside diameter of 0.8 mm and a length of 20 mm. A Beckman Model 4500 pH meter (Beckman Instruments Inc, Irvine,

CA) with a temperature controlled pH unit was used to continuously monitor changes in the interstitial pH during the ischemic period. The electrode was positioned at an angle of approximately 45 degrees to the epicardial surface at a depth of 6 to 8 mm.

Electrode Calibration Procedure

The miniature pH electrode was calibrated with standard laboratory buffers (BDH Chem, Poole, UK) of pH 4.00 and 7.00 at different temperatures ranging from 10° to 20°C. The mean response time to a step change in pH was 35 seconds. The electrode was calibrated before each experiment.

Myocardial Temperature Measurements

Myocardial temperature was measured continuously with thermoneedle probes (Model 6500; Mon-a-Therm Inc, St. Louis, MO) placed in the right and left ventricular muscle wall (next to the pH electrode) and the ventricular septum.

Experimental Preparation and Protocol

All animals were anesthetized intravenously with sodium pentobarbital (30 mg/kg), intubated, and ventilated with a volume-controlled Penlon 2000 respirator. Anesthesia was maintained with a mixture of oxygen and halothane (Fluothane; Wyeth-Ayerst Laboratories, Philadelphia, PA).

The left femoral artery was cannulated for monitoring systemic blood pressure, arterial blood gases, and hematocrit values. Systemic temperature was monitored with a rectal temperature probe connected to the Sarns 2200 operating console. The electrocardiogram was monitored continuously throughout the experiment.

A midline sternotomy was performed after systemic heparinization (5 mg/kg), and the aorta was cannulated with an 18F Argyle cannula. Both the superior and inferior venae cavae were cannulated and snared for venous return. The coronary sinus was cannulated through the right atrium to sample coronary venous blood samples. The azygos drainage was excluded from the venous return by passing a snare around the azygos vein. The left ventricle was vented through a 16F venous cannula positioned through a pursestring-sutured stab wound in the apex. A 10F coronary perfusion cannula was inserted into the ascending aorta to administer the cardioplegic solutions after aortic cross-clamping.

Before cardiopulmonary bypass, myocardial tissue pH, myocardial temperature, and intracardiac pressures were measured and blood samples were drawn from the femoral artery and coronary venous drainage to obtain pre-ischemic control values.

Cardiopulmonary bypass was established with the use of a Harvey (Model H-1300; William Harvey Research Corp, Santa Ana, CA) bubble oxygenator gassed with 95% oxygen and 5% carbon dioxide. Arterial pH was maintained between 7.35 and 7.45, carbon dioxide tension between 35 and 45 mm Hg, and oxygen tension greater than 120 mm Hg.

At total cardiopulmonary bypass flow, systemic hypo-

thermia was introduced and the arterial temperature lowered to 17°C. At this point, the aorta was cross-clamped for 150 minutes and the specific method of myocardial preservation was introduced. In group I, only hypothermia was used as a method of myocardial protection. Myocardial tissue temperature was controlled at $15^{\circ} \pm 1^{\circ}\text{C}$ with the aid of systemic hypothermia and topical cooling. In group II (THAM) and III (bicarbonate), 450 mL of cardioplegic solution at $14^{\circ} \pm 2^{\circ}\text{C}$ was immediately administered at a constant perfusion pressure of 80 mm Hg. Supplementary 225-mL doses of cardioplegic solution were administered every 30 minutes. In group IV, the myocardium was immediately perfused with 450 mL of cold ($12^{\circ} \pm 1^{\circ}\text{C}$), hyperkalemic, oxygenated blood (oxygen tension > 125 mm Hg) at 80 mm Hg. This procedure was repeated every 30 minutes with 225 mL of hyperkalemic blood. In group V, St. Thomas 2 solution was oxygenated with 95% oxygen and 5% carbon dioxide (oxygen tension > 400 mm Hg; pH = 7.8 at 15°C). An initial dose of 450 mL was administered at 80 mm Hg, followed by 225-mL doses every 30 minutes. The final dose was administered at 120 minutes.

Care was taken to maintain the myocardial tissue temperature at $15^{\circ} \pm 1^{\circ}\text{C}$ in all five groups for 120 minutes. Rewarming started at 120 minutes in all five groups. At 150 minutes of ischemia, normothermia ($36^{\circ} \pm 1^{\circ}\text{C}$) was accomplished and the aorta was unclamped.

After electromechanical activity resumed, stabilization on total bypass in the beating empty state was allowed for 15 minutes. Normal hemodynamic function was reintroduced and cardiopulmonary bypass stopped. Hemodynamic data were recorded, tissue pH was measured, and blood samples were taken at 15-minute intervals. At the end of the experiment, biopsy specimens were obtained for myocardial tissue water content and morphologic examination.

Hemodynamic Functional Assessment

Two 18-gauge catheters were inserted into the left atrium and left ventricle to measure corresponding pressures before and after the cardioplegic period.

Left atrial filling pressure was stabilized at 8 ± 1 mm Hg by controlling the venous return through the cardiopulmonary bypass volume. Left ventricular systolic, left ventricular end-diastolic, and left atrial filling pressure were measured before bypass (control) and at 15, 30, and 45 minutes after ischemia. Myocardial function was assessed by determination of developed pressure in the left ventricle and expressed as a percentage of the prearrest developed pressure.

Biochemical Measurement

Myocardial creatine kinase levels were measured as an indicator of metabolic changes taking place during ischemia. Samples of the coronary venous effluent were taken before bypass (control) and during every cardioplegic infusion. Analyses were done on a Baker Scientific spectrophotometer (Baker Scientific Instruments, NY) and expressed as international units per liter.

Morphological Examination

Myocardial tissue biopsy samples were taken before bypass to examine the normal morphology of the myocardium at the electron microscopic level. Additional biopsy samples taken at the end of each experiment were used to assess morphologic changes resulting from the ischemic period. A devised, semiquantitative grading system [25] based on well-established criteria of early myocardial ischemic injury was used to assess ultrastructural changes. The histologic observer was unaware of the experimental group during observation. All samples were obtained from actively contracting regions of the left ventricle within 1 cm of the pH electrode.

The samples were immediately placed in a fixative solution of 3% glutaraldehyde in phosphate buffer for 24 hours and postfixed in 1% buffered (Palade) osmium tetroxide for 1 hour. The samples were then dehydrated in a graded series of acetone, embedded in Spurr's epoxy resin and cut into 60- to 80-nm-thick sections. The sections were mounted on copper grids and routinely stained for transmission electron microscopy with uranyl acetate and lead citrate.

Myocardial Water Content

Myocardial water content was determined by weighing the biopsy samples (Mettler ME-22 analytical scale; Mettler Instrument Corp, Hightstown, NJ) before desiccation at 75°C for 24 hours. Percent water content was calculated as: $100 \times (\text{wet weight} - \text{dry weight})/\text{wet weight}$.

Statistical Analysis

All values are expressed as mean $\pm$ standard error of the mean. The data were analyzed with a one-way analysis of variance, and differences between groups were identified with Tukey's "Studentized range." A p value of less than 0.05 was considered significant.

Results

Myocardial Temperature

Preischemic left ventricular temperatures were similar in all five groups ($37^{\circ} \pm 1.23^{\circ}\text{C}$). From 0 to 120 minutes of ischemia, temperatures ranged from $15.01^{\circ} \pm 1.32^{\circ}\text{C}$ up to $16.06^{\circ} \pm 1.04^{\circ}\text{C}$ (Fig 1). No significant difference ($p > 0.05$) existed between groups. After the rewarming phase at 150 minutes of ischemia, the ventricular temperatures ($36^{\circ} \pm 1^{\circ}\text{C}$) were similar in the five groups.

Myocardial pH

In the entire group, the interstitial pH rose from 7.12 ± 1.02 to 7.25 ± 1.3 as systemic hypothermia of 17°C was reached. After cross-clamping, there was a progressive decrease in interstitial pH in group I, in which hypothermia only was used. In groups II to V an immediate increase in interstitial pH followed the infusion of the initial dose of cardioplegia (Fig 2).

Thereafter, pH levels progressively decreased in all five groups during the 30-minute interval, resulting in a pH of 6.71 ± 0.18 in group I, 7.17 ± 0.04 in group II, 7.11 ± 0.05 in group III, 7.06 ± 0.07 in group IV, and 7.34 ± 0.04 in

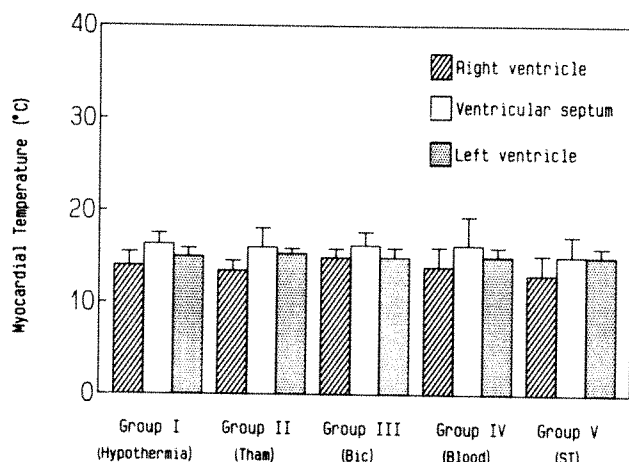


Fig 1. Myocardial temperature measured in the respective groups during 150 minutes of ischemia. All values are expressed as mean $\pm$ standard error of the mean ($p > 0.05$ for difference between groups). (Bic = bicarbonate; ST = St. Thomas; Tham = Tris hydroxymethyl aminomethane.)

group V. In group I, the pH continued to decline in a linear relationship with ischemic time.

With the infusion of the second dose of cardioplegia at 30 minutes, the interstitial pH in groups II to V rose sharply. Between 30 and 60 minutes ischemia, decline in pH levels in groups II and IV were less prominent compared with that of groups III and V.

This fluctuating pattern in interstitial pH levels continued throughout the 120 minutes of ischemia in groups II to V. At 120 minutes of ischemia, the pH in group I (6.40 ± 0.07) differed significantly ($p < 0.001$) from that of the remaining groups. The pH in group II (7.23 ± 0.05) and group IV (7.27 ± 0.07) differed significantly ($p < 0.05$) from that of group III (7.14 ± 0.02) and group V (7.02 ± 0.05).

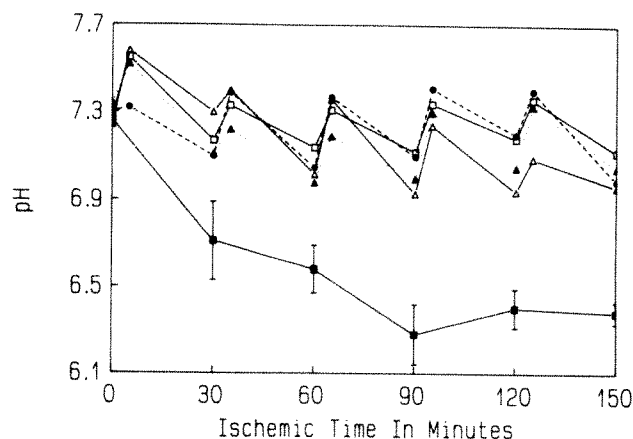


Fig 2. Interstitial pH changes in the left ventricle recorded in all five groups during 150 minutes of ischemia ($p < 0.01$ for the difference between hypothermia and the rest of the cardioplegic groups). (Solid square = hypothermia; open square = THAM-buffered blood cardioplegia; solid triangle = bicarbonate-buffered blood cardioplegia; solid circle = hyperkalemic blood; open triangle = St. Thomas 2.)

Table 2. Left Ventricular Developed Pressure Before Ischemia and at 15, 30, and 45 Minutes After Reperfusion at a Left Atrial Pressure of 8 ± 1 mm Hg^a

Group	Before Ischemia	15 minutes	30 minutes	45 minutes
Group I	96 $\pm$ 3	24 $\pm$ 2	30 $\pm$ 6	23 $\pm$ 4
Group II	95 $\pm$ 3	69 $\pm$ 4	80 $\pm$ 8	87 $\pm$ 3
Group III	98 $\pm$ 2	65 $\pm$ 3	69 $\pm$ 6	80 $\pm$ 4
Group IV	96 $\pm$ 3	68 $\pm$ 3	74 $\pm$ 3	80 $\pm$ 6
Group V	96 $\pm$ 2	72 $\pm$ 3	66 $\pm$ 4	63 $\pm$ 4

^a Values are the mean $\pm$ standard error of the mean in millimeters of mercury; $p > 0.05$ for values before ischemia.

During the rewarming phase, the pH in group I decreased from 6.40 ± 0.07 to 6.38 ± 0.05 , in group II from 7.23 ± 0.05 to 7.12 ± 0.02 , in group III from 7.14 ± 0.02 to 7.05 ± 0.04 , in group IV from 7.27 ± 0.03 to 6.99 ± 0.04 and in group V from 7.02 ± 0.02 to 6.96 ± 0.04 .

Hemodynamic Functional Assessment

Table 2 presents left ventricular developed pressure measured before ischemia and at 15, 30, and 45 minutes after reperfusion.

Left ventricular systolic function measurements as represented by developed pressure (percent control) and end-diastolic pressure changes are shown in Figures 3 and 4, respectively. Recovery of developed pressure in group I was severely depressed (unable to be weaned from bypass) and significantly less ($p < 0.05$) than that of groups II to V during the entire period after reperfusion. No significant difference ($p > 0.05$) was noted between groups II to V 15 minutes after reperfusion. At 30 minutes after reperfusion, group II had a significant improvement ($p < 0.05$) in recovery compared with that of the remaining groups. At 45 minutes, the pattern of recovery was unchanged except that group V had deteriorated function and differed significantly ($p < 0.05$) from groups III and IV.

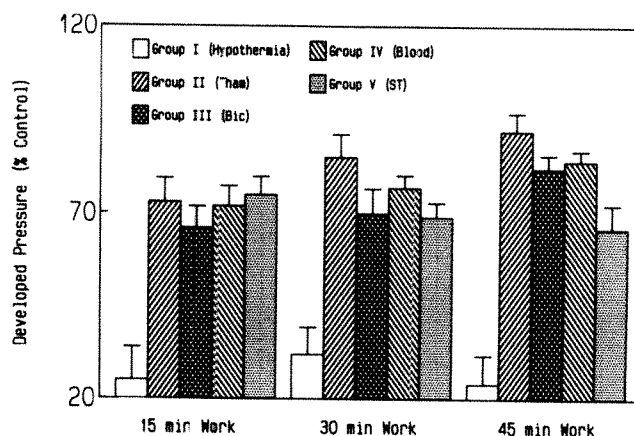


Fig 3. Postischemic left ventricular function expressed as a percentage of the prebypass (control) developed pressure (mean $\pm$ standard error of the mean; p values as stated in text). (Abbreviations are as in Figure 1.)

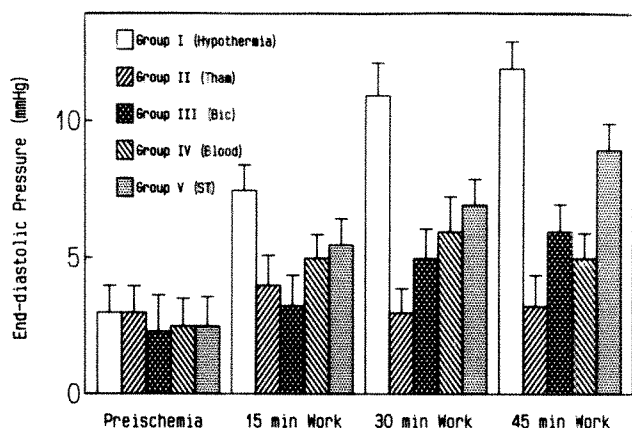


Fig 4. Left ventricular end-diastolic pressure measured at 15, 30, and 45 minutes after reperfusion (mean $\pm$ standard error of the mean; p values as stated in text). (Abbreviations are as in Figure 1.)

Preischemic left ventricular end-diastolic pressure ranged between 2.2 ± 0.9 and 3.0 ± 0.8 mm Hg in groups I to V. At 15 minutes after reperfusion, the elevated pressure in group I differed significantly ($p < 0.02$) from that of groups II to V. At 30 minutes, these pressures increased to 11.1 ± 1.0 mm Hg in group I, decreased to 3.0 ± 0.6 mm Hg in group II, and were slightly elevated in groups III to IV.

At 45 minutes, the most prominent increase in left ventricular end-diastolic pressure was noticed in group I. At the same time the left ventricular end-diastolic pressure returned to normal values in group II.

Biochemical Measurement

Preischemic myocardial creatine kinase levels were similar in all five groups (mean, 81 ± 12 IU/L). The creatine phosphokinase level was significantly ($p < 0.01$) increased in group I at 30 and 60 minutes of ischemia. No significant difference ($p > 0.05$) existed between groups II to V (Fig 5). From 90 to 120 minutes of ischemia, groups IV and V differed significantly ($p < 0.05$) from groups II and III. After rewarming at 150 minutes, a marked increase was

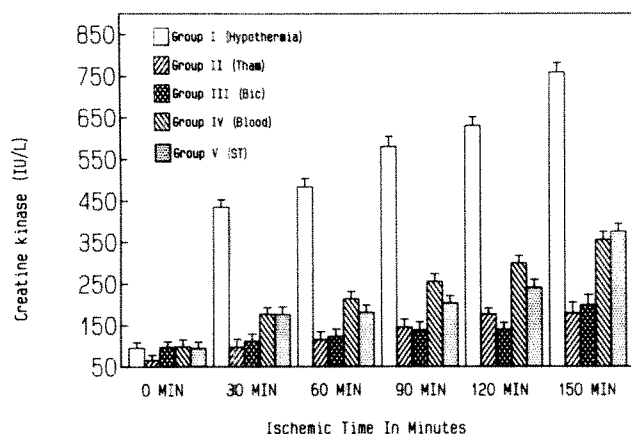


Fig 5. Creatine kinase levels in the coronary venous effluent (mean $\pm$ standard error of the mean; p values as stated in text). (Abbreviations are as in Figure 1.)

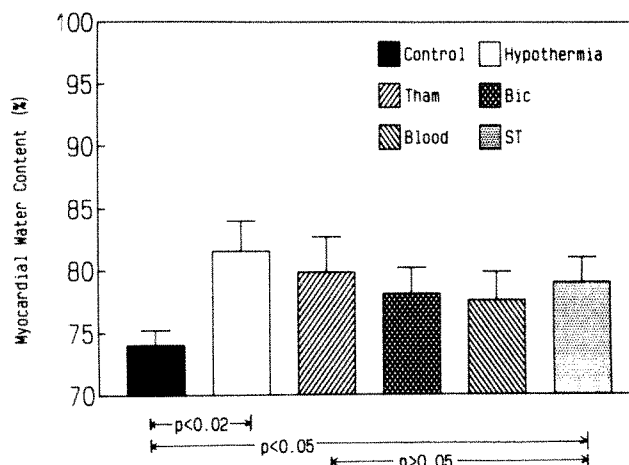


Fig 6. Myocardial water content measured 45 minutes after reperfusion and expressed as a percentage (mean $\pm$ standard error of the mean; $p < 0.05$ for difference between control and cardioplegic groups; $p > 0.05$ for difference between the cardioplegic groups). (Abbreviations are as in Figure 1.)

present in groups I, IV, and V. In groups II and III, the increase was less prominent.

Myocardial Water Content

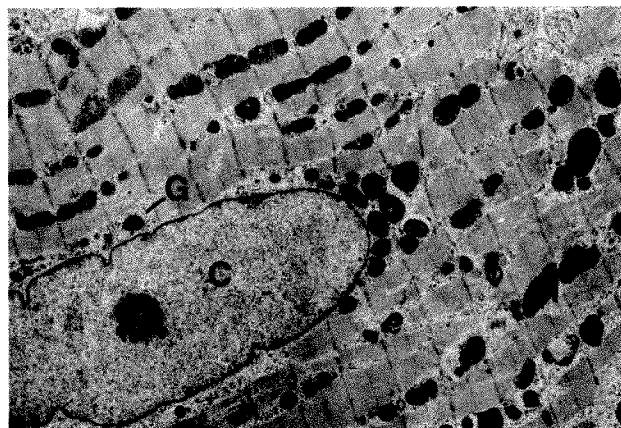
Preischemic biopsy samples of the left ventricle revealed a water content of $74.0\% \pm 2.03\%$ in all five groups (Fig 6). A significant increase ($p < 0.02$) in myocardial water content was present in group I compared with the control at the end of the reperfusion period. Myocardial water content in groups II to V was $79.86\% \pm 2.85\%$, $78.15\% \pm 2.07\%$, $77.85\% \pm 1.80\%$, and $79.03\% \pm 1.99\%$, respectively ($p > 0.05$).

Morphological Examination

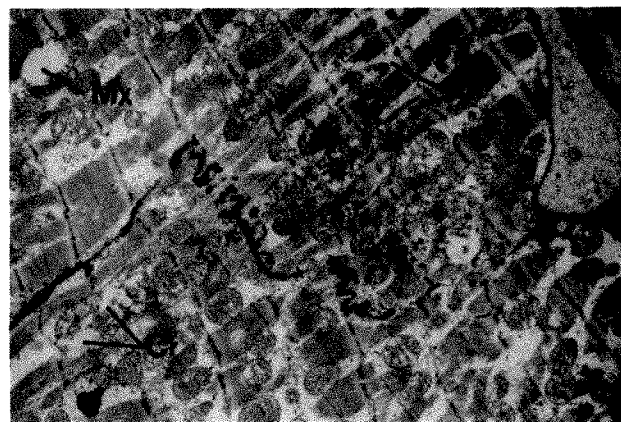
Tissue biopsy samples taken before ischemia indicated normal morphology of the myocytes with no ultrastructural changes (Fig 7A). After 150 minutes of ischemia and 60 minutes of reperfusion, severe ischemic injury appeared in group I. This injury was evident by marked mitochondrial swelling, disruption of the cristae, clearing of the matrix, and intracellular edema (Fig 7B). Biopsy samples taken from groups II to V appeared relatively normal with only slight ultrastructural changes. Figure 7C represents an overall view of these minor changes. Slight mitochondrial swelling, almost no ruptured cristae, and intracellular edema attest to the normal ultrastructure of these groups.

Comment

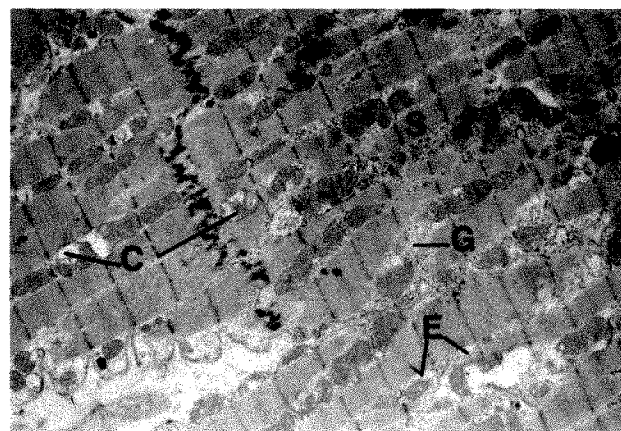
Myocardial protection afforded by hypothermic potassium-based cardioplegic solutions is well established in the experimental and clinical settings [26, 27]. Most of these solutions are formulated to retard myocardial metabolic processes in an effort to reduce the demand for high-energy phosphates and oxygen. However, these processes are not suppressed entirely, and anaerobic metabolites still accumulate [28]. Efforts to minimize the



A



B



C

Fig 7. (A) Ultrastructural assessment of the left ventricle, sampled before bypass at normothermia. The myocyte appears normal with normal shaped mitochondria (M), fine dispersed chromatin (C) in the nucleus, and no intramyofibrillar or intermyofibrillar edema. Glycogen granules (G) are well dispersed in the intermyofibrillar sarcoplasm. ($\times 7,540$ before 38% reduction.) (B) Ultrastructural assessment of the left ventricle, sampled 45 minutes after reperfusion in group I. Marked ischemic injury with ruptured cristae (Cr), clearing of the matrix (Mx), and severe intramyofibrillar and intermyofibrillar edema (E) is visible. ($\times 7,540$ before 38% reduction.) (C) Representative sample of the ultrastructural morphology of the left ventricle, sampled 45 minutes after reperfusion in groups II to V. Minor ultrastructural changes with only disrupted cristae (Cr) in a few mitochondria and slight intermyofibrillar edema (E) are visible. The sarcomeres (S) are relaxed, and glycogen (G) is present. ($\times 7,540$ before 38% reduction.)

accumulation of these metabolites by means of multidose cardioplegic infusion with low buffer capacity have been reported to be unsuccessful [29]. This finding was further complemented by observations by Lai and Scheuer [30] that intracellular acidosis and accumulation of lactate occur even when the myocardium is continuously perfused with hypoxic crystalloid solutions. Reports by Tait and co-workers [31] proved that multidose infusion of Bretschneider's solution was highly effective in preventing tissue acidosis for more than 60 minutes.

In this study we demonstrated the advantage of an effective buffer over that of a weakly buffered cardioplegic solution at moderate hypothermic conditions. Moderate hypothermia alone proved to be unsuccessful in preventing tissue acidosis. Buffered cardioplegic solutions and nonbuffered hyperkalemic blood substantially altered myocardial tissue acidosis. The superior effect of THAM-buffered blood cardioplegia supports the findings of previous reports.

THAM is a strong buffer and, when combined with oxygenated blood, forms an extremely efficient buffering system in the presence of blood serum proteins and hemoglobin, a prime source of histidine. Furthermore, red blood cells contain carbonic anhydrase, which facilitates transfer of CO_2 from the tissue to the blood by creating a gradient due to rapid removal of CO_2 in the red blood cells. An added advantage of blood cardioplegia is its capacity to supply oxygen for aerobic glycolysis. The inadequacy of the bicarbonate-buffered solutions to prevent interstitial acidosis underscores the findings of Warner and associates [32].

The effective protection afforded by hyperkalemic blood can be related to the intermittent washout of H^+ ions and lactate and the excellent buffering capacity of blood during prolonged infusions. Furthermore, the oxygen supplied by the blood could entertain brief periods of oxidative metabolism during which some of the accumulated lactate can be used to produce adenosine triphosphate.

In group I, functional recovery could not be obtained. In this group and the remaining groups, functional recovery was consistent with the pH changes observed during the ischemic period. This phenomenon supports Bretschneider's hypothesis concerning the buffering capacity of a cardioplegic solution.

Although elevated creatine kinase levels did reflect the influence of ischemic injury in all five groups, no significant correlation existed between these changes and postischemic function.

The increase in myocardial water content probably reflects damage to the volume-regulating capacity of the myocardial cells during the ischemic period. The significant increase in myocardial water in group I emphasizes the protecting effect of a buffered solution during ischemia at moderate hypothermic conditions.

The ultrastructural changes seen in the different groups complemented the aforementioned findings. In group I, extreme intracellular edema and cell disarrangement were evident due to the increased myocardial water content. Normal ultrastructure found in the remaining groups correlates well with postreperfusion functional recovery.

In conclusion, moderate hypothermia alone is ineffec-

tive in preventing interstitial acidosis. The effect of strongly buffered blood-based cardioplegic solutions is superior to that of weakly buffered blood-based solutions as well as that of buffered crystalloid solutions in maintaining interstitial pH and consequently myocardial function. Interstitial pH is an indicator of the severity of progressive ischemic injury, and we suggest that continuous intraoperative interstitial pH monitoring could be of value in assessing the myocardial status at all times during this critical phase of the operation.

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Autologous Vein Supported With a Biodegradable Prosthesis for Arterial Grafting

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To evaluate the potential of a supporting, compliant, biodegradable prosthesis to function as a temporary protective scaffold for autologous vein grafts in the arterial circulation, we implanted vein grafts into the carotid arteries of rabbits, either with (composite grafts) or without (control grafts) such a supporting prosthesis, and evaluated them up to 6 weeks. The control vein grafts showed edema and severe medial disruption with infiltration of polymorphonuclear cells on day 1. Over the study, irregular fibrocyte formation resulted in the

formation of a fibrotic vein wall. In contrast, the composite vein grafts showed preservation of smooth muscle cell layers and elastic laminae with a minor inflammatory response. Regular proliferation of fibroblasts, which in some areas were circularly oriented, was observed. We conclude that a supporting, compliant, biodegradable prosthesis can function as a protective scaffold for vein grafts in the arterial circulation, thus reducing damage to the vein graft wall and allowing gradual arterialization.

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When used as an arterial substitute, autologous vein grafts undergo degenerative changes during long-term implantation [1, 2]. This is reflected by their low long-term patency rate compared with the patency rate of arterial autografts [3]. The degenerative changes in the vein wall might have their origin in the early postoperative period. After implantation, the vein wall shows a certain degree of deendothelialization and medial damage, including disruption, fibroblast transformation of smooth muscle cells, and an inflammatory response in the vein wall with edema [4-6]. All these changes are alleged to lead to progressive fibrosis, intimal hyperplasia, and atherosclerosis of the vein wall [4, 5].

Factors such as exposure to storage media [7, 8], surgical trauma [9, 10], ischemia resulting from the interruption of vasa vasorum [5, 6], and sudden exposure to the higher arterial pressure, resulting in overstretching of the vein wall [9, 11, 12], are involved in early damage and changes of the vein wall. With special storage media and a surgical "no-touch" technique, this "iatrogenic" damage can be reduced [9, 13, 14]. However, damage to the vein graft caused by unavoidable ischemia and overstretching of the vein wall remains.

This study was undertaken to evaluate the potential of a supporting, compliant, biodegradable prosthesis to function as a temporary protective scaffold for autologous vein grafts when implanted into the arterial system. Such a protective scaffold might prevent overstretching and allow gradual adaptation to arterial pressures, ie, gradual

arterialization of the vein graft. In previous studies, we [15-19] have already demonstrated the good healing characteristics of such biodegradable prostheses.

Material and Methods

Male Chinchilla rabbits ($n = 34$) weighing 3.5 to 4 kg were used for microsurgical implantation of both a control autologous vein graft and a composite vein graft composed of autologous vein supported with a compliant, biodegradable prosthesis [15]. The side of implantation (ie, right or left carotid artery) was randomized. All animals used in this study received humane care in compliance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research and the "Guide for the Care and Use of Laboratory Animals" prepared by the National Academy of Sciences and published by the National Institutes of Health (NIH Publication No. 85-23, revised 1985).

Biodegradable Prosthesis

The compliant, biodegradable prostheses were prepared from 90/10 (wt%) polyurethane/poly-L-lactic acid. The prostheses had an internal diameter of 2.5 mm, a length of 1.5 cm, and a pore size gradient in their 0.3-mm-thick graft wall ranging from 30 μm in the inner region of the graft lattice to 100 μm in the outer region. All prostheses were sterilized with ethylene oxide and evacuated for 24 hours under high vacuum (10 to 5 mm Hg). Degradation of these prostheses is primarily a matter of fragmentation [20].

Surgical Technique

The rabbit was anesthetized by an intravenous injection of sodium pentobarbital (Nembutal; Abbott Laboratories,

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North Chicago, IL; 30 mg/kg) into the marginal ear vein. The animal also was intubated, and inhalation anesthesia was accomplished with 1% halothane (Fluothane; Wyerth-Ayerst).

Under sterile conditions, a ventral midline incision was made in the neck, and the carotid arteries were carefully exposed. A 1-cm segment with a diameter of 2 mm (± 0.1 mm) from a branch of the external jugular vein at the mandibular area was used as the control vein graft. This vein graft matched in size with the carotid artery after clamp release. A 1-cm segment with a diameter of 3.2 mm (± 0.1 mm) from the internal jugular vein was used as the autologous vein graft to create the composite vein graft. All vein grafts were stored for 5 minutes in heparinized saline solution. Then all vein grafts were implanted in the carotid arteries with end-to-end anastomoses by means of standard microsurgical techniques [19].

To implant the composite vein graft, the exposed carotid artery was first clamped proximally and distally and cut in the middle. Then the distal clamp was released, and the prosthesis (internal diameter, 2.5 mm) was slipped over the distal part of the carotid artery. After implantation of the vein graft, the prosthesis was shifted back over the vein graft, including both anastomoses, thus reducing the diameter of the vein graft from 3.2 mm (± 0.1 mm) to 2.5 mm and forming a composite vein graft. Interrupted sutures of 9-0 Ethilon on a BV-4 needle (Ethicon, Somerville, NJ) were used to make the vessel anastomoses. The mean carotid artery cross-clamp time was 25 minutes.

After hemostasis had been secured by gentle pressure, a solution of lidocaine hydrochloride was applied at the proximal and distal anastomoses to prevent spasm of the carotid artery. Patency was determined by direct inspection for arterial pulsation. After the operation on both carotid arteries, the wound was irrigated with saline solution and closed with 2-0 Dexon.

The rabbits were housed individually under controlled environmental conditions with free access to water and normal L.K.K. pellet rabbit food (Hope Farms BV, Woerden, the Netherlands). They did not receive any anticoagulants.

Graft Evaluation and Harvesting Procedure

The grafts were evaluated at 1 day ($n = 6$ rabbits), 1 week ($n = 6$), 2 weeks ($n = 6$), 3 weeks ($n = 8$), and 6 weeks ($n = 8$) after operation. The rabbits were then anesthetized with pentobarbital (Nembutal; 30 mg/kg body weight, administered intravenously). The composite vein grafts and control vein grafts were carefully dissected free, and heparin sodium (1,000 IU, intravenously) was given to prevent clotting caused by the harvesting procedure. All grafts were gently perfused with 6.8% sucrose solution in 0.1 mol/L cacodylate buffer and then fixed by pressure-controlled perfusion (100 mm Hg) with 2% glutaraldehyde in 0.1 mol/L cacodylate buffer.

Each of the fixed specimens was divided into two equal segments. Each segment was then prepared for and evaluated by routine light or scanning electron microscopy. Both forms of microscopy were used for morpho-

logic evaluation of the endothelial lining. Light microscopy was used for morphologic evaluation of the graft walls, the subendothelial smooth muscle cell layers as well as the adventitia.

Preparation for Scanning Electron Microscopy

The grafts, fixed by pressure-controlled perfusion, were dissected and left in the same fixative for 24 hours at 4°C. Next, the specimens were rinsed for 30 minutes in 6.8% sucrose solution in 0.1 mol/L cacodylate buffer, pH 7.4, to remove excess glutaraldehyde and postfixed for 3 hours in 1% osmium tetroxide in 0.1 mol/L cacodylate buffer, pH 7.4, at 4°C. After dehydration in an ethanol series up to 100%, the specimens were dried to the critical point with liquid carbon dioxide. Then they were cut into two or three longitudinal segments and sputter coated with gold (15 nm). These segments were examined in an ISI-DS-130 scanning electron microscope operated at 7 to 10 kV.

Preparation for Light Microscopy

The specimens were dehydrated in alcohol. After immersion in Technovit 8100 (Kulzer GmbH, Wehrheim, Germany) overnight, they were embedded in 40 mL of Technovit 8100 (solution A) and in 1 mL of the hardener Technovit 8100 (solution B). After polymerization at room temperature, semithin (2 μ m) sections were routinely cut and stained with hematoxylin and eosin and elastin stain (Verhoeff's stain).

Results

Unimplanted Vein Grafts

Unimplanted external (control) and internal jugular vein grafts (as in the composite vein grafts) consisted of an endothelial layer, an incomplete internal elastic lamina, a media with one to two layers of smooth muscle cells, and an adventitia composed of collagen. Both media and adventitia contained thin elastic laminae.

Control Vein Grafts

On day 1, the control vein grafts were deendothelialized over approximately 80% of the graft surface. The thin smooth muscle cell layers were completely disrupted, and many polymorphonuclear cells (PMNs) had infiltrated into the edematous wall (Fig 1a). Fragments of thin elastic laminae were observed in the vein wall (Fig 1c).

At 1 week, reendothelialization had occurred over approximately 50% of the graft surface. Disruption of the vein wall and edema with many PMNs were still observed (Fig 2a).

At 2 weeks, all control vein grafts were completely reendothelialized. At this time, as well as at 3 weeks, irregularly oriented fibrocytes had partly replaced the areas of disruption with PMNs (Fig 3a). Elastic laminae were no longer seen (Fig 3c). At 6 weeks, all areas of inflammation in the control vein grafts were completely replaced by mature fibrous tissue with an irregular structure (Fig 4a).

Composite Vein Grafts

The composite vein grafts were also deendothelialized over approximately 80% of the graft surface on day 1.

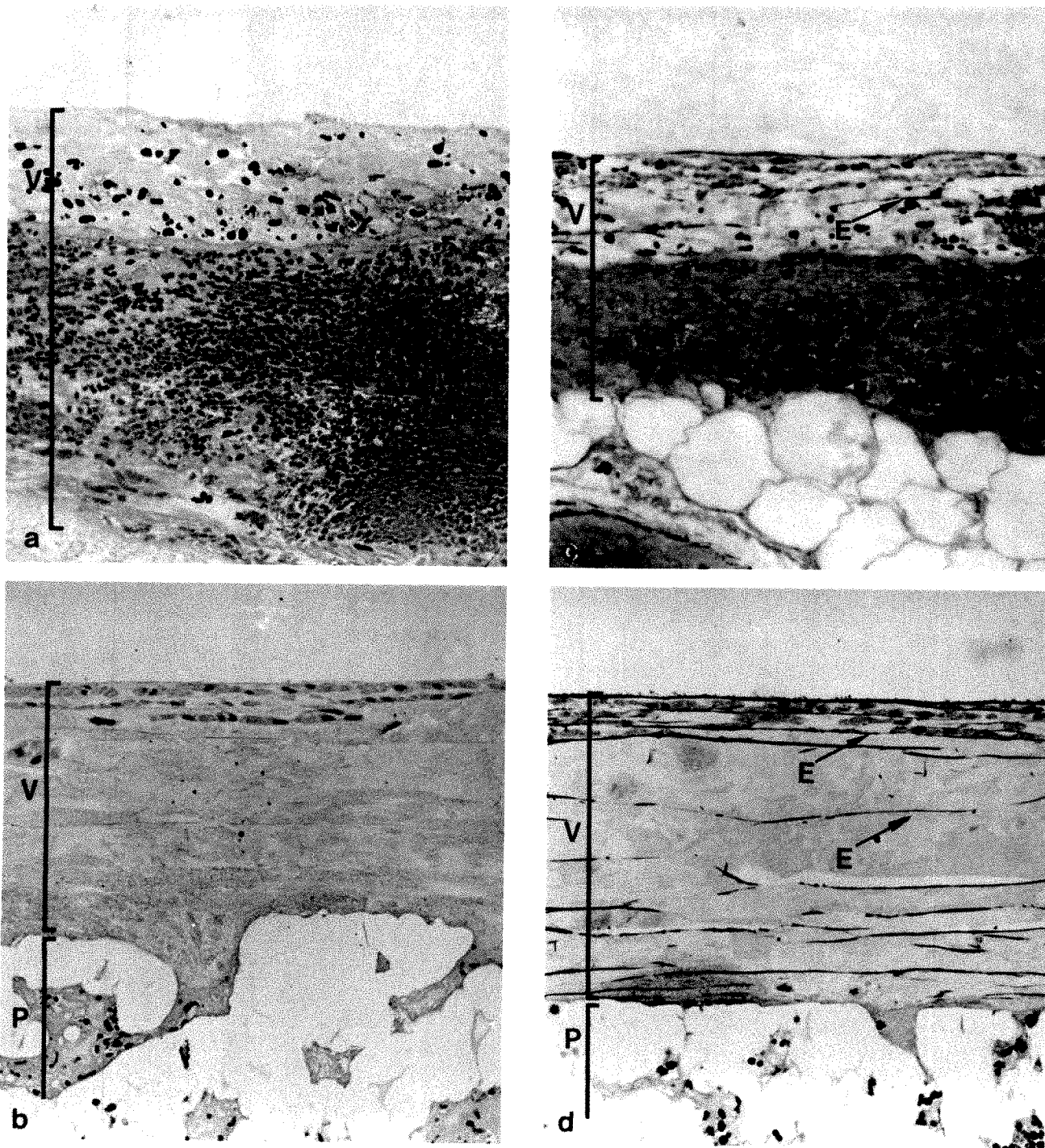


Fig 1. Light micrographs of (a, c) a control vein graft and (b, d) a composite vein graft 1 day after implantation. (a) In the control vein graft, there is complete disruption of smooth muscle cell layers with infiltration of many polymorphonuclear cells into the edematous vein wall. (b) In the composite vein graft, most smooth muscle cell layers are preserved. The vein wall is edematous. (c) In the control vein graft, only fragments of elastic laminae are present. (d) Elastic laminae are preserved in the composite vein graft. (a and b, nematoxylin and eosin; c and d, elastin stain [Verhoeff's stain]; all, $\times 250$.) (E = elastic laminae; P = prosthesis; V = vein wall.)

Although partial disruption of the smooth muscle cell layers was observed, most of them were still preserved and were arranged longitudinally. The vein wall had an edematous appearance in the deep layers but showed significantly less PMN infiltration than the control vein

grafts (Fig 1b). The thin elastic laminae normally present in the vein wall were preserved (Fig 1d).

At 1 week, the composite vein grafts were reendothelialized over approximately 75% of their surface. The vein wall by then showed regular layers of longitudinally

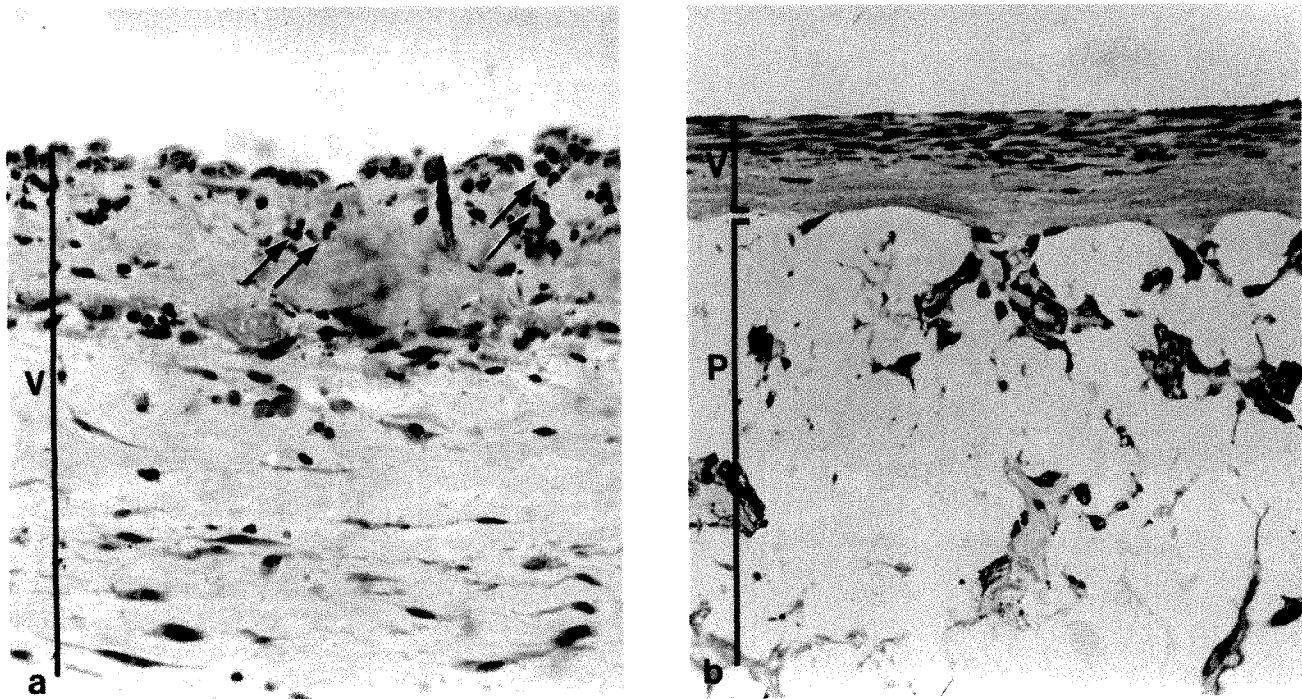


Fig 2. Light micrographs of (a) a control vein graft and (b) a composite vein graft 1 week after implantation. (a) Note the disruption of the smooth muscle cell layers in the control vein graft. Polymorphonuclear cells (arrows) are abundant in the edematous vein wall. (b) In contrast, the composite vein graft shows regular layers of immature fibroblasts with only a few polymorphonuclear cells. (Hematoxylin and eosin; $\times 250$.) (P = prosthesis; V = vein wall.)

oriented, immature fibroblasts with few PMNs (Fig 2b). Edema had disappeared, and thin elastic laminae were present. The prosthesis was surrounded and infiltrated by many macrophages and multinuclear giant cells.

At 2 weeks, endothelial coverage was complete. The vein wall had regular layers of longitudinally oriented, immature fibroblasts with only a very few PMNs. Thin elastic laminae were still present in the vein wall. Many macrophages and multinuclear giant cells were observed in and around the prosthetic material.

At 3 weeks, the vein wall had a similar aspect, but no PMNs were present (Figs 3b, 3d). By then, the prosthesis had started to fragment. At 6 weeks, the vein wall had gradually arterialized; it had increased in thickness and consisted of eight to 12 layers of immature fibroblasts. Moreover, in some areas, these layers had a prevalence for circular orientation (Fig 4b). Thin elastic laminae were observed but were less pronounced. Fragmentation of the prosthesis had continued slowly, and many macrophages and multinuclear giant cells were present.

Comment

The present study demonstrates that a compliant, biodegradable prosthesis can indeed function as a protective scaffold for autologous vein grafts when implanted into the arterial circulation: the prosthesis prevents overstretching of vein grafts, preventing subsequent damage [21]. We observed the preservation of smooth muscle cell layers and elastic laminae and only a minor inflammatory

reaction with few PMNs in the vein wall after 1 day of implantation. Moreover, the slowly degrading prosthesis allowed regular and gradual arterialization of the vein wall. In contrast, the unsupported control vein graft wall was completely disrupted after 1 day of implantation and showed severe inflammatory reaction of PMNs and edema. The walls healed with the formation of mature fibrous tissue without elastic laminae, resulting in fibrosis of the vein wall at 6 weeks.

The early changes observed in our control vein grafts resemble the changes described in coronary artery vein grafts in humans. After implantation, a large degree of deendothelialization occurs, and the media shows disruption of smooth muscle cell layers with edema and leukocyte infiltration [4-6]. All these changes in the vein wall might originate from damage to the vein graft during preparation [7, 8] or implantation [9, 10] and from ischemia [5, 6] and overstretching by the higher arterial pressures [9, 11, 12]. Regeneration occurs with reendothelialization and progressive medial fibrosis [4-6], as was observed in our control vein grafts. Later changes include intimal hyperplasia and atherosclerosis [4, 5].

Although many growth factors and enzymes might be involved in this process, a key role in the pathogenesis of vein graft degeneration is attributed to platelet-derived growth factor. It can be released not only by platelets but also by endothelial cells, smooth muscle cells, and monocytes [22-24].

To date, little attention has been paid to the influence on vein graft degeneration of the inflammatory reaction of

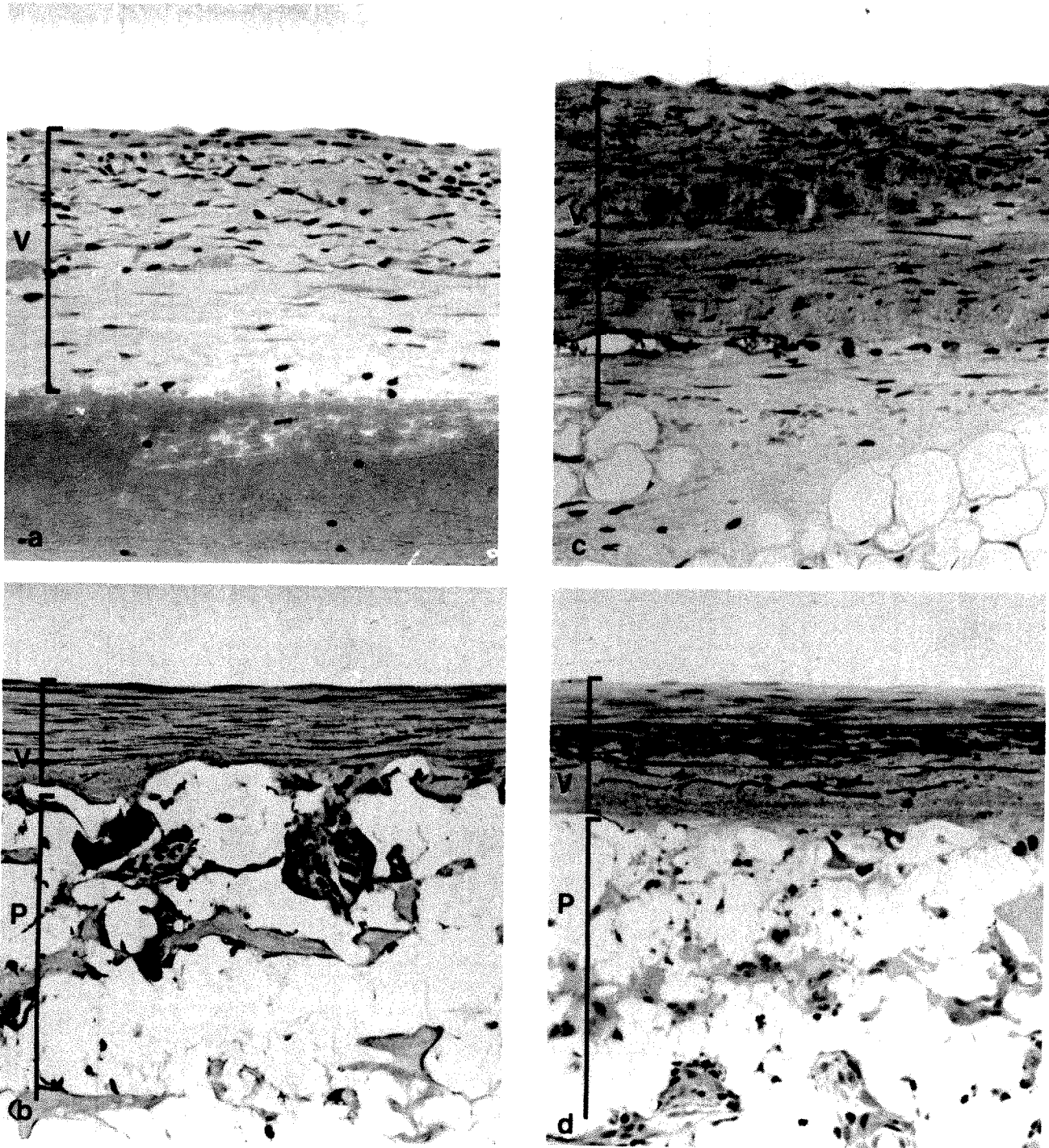


Fig 3. Light micrographs of (a, c) a control vein graft and (b, d) a composite vein graft 3 weeks after implantation. (a) Note the irregular arrangement of fibrocytes in the control vein graft. (b) The composite vein graft shows regular proliferation of immature fibroblasts. (c) In the control vein graft, elastic laminae have completely disappeared. (d) In the composite vein graft, elastic laminae are present. (a and b, hematoxylin and eosin; c and d, elastin stain [Verhoeff's stain]; all, $\times 250$.) (P = prosthesis; V = vein wall.)

PMNs in the vein wall caused by the disruption of the smooth muscle cell layers after implantation. In our rabbit model, the severe inflammatory reaction with PMNs in the disrupted layers of the control vein grafts was especially striking and lasted for the first 3 weeks in contrast to

the composite vein grafts. These activated PMNs release several enzymes, including elastase and collagenase [25]. These enzymes lyse, among others, elastic laminae and collagen, further destroying the integrity of the vein graft matrix. These inflammatory processes lead to fibrosis, as

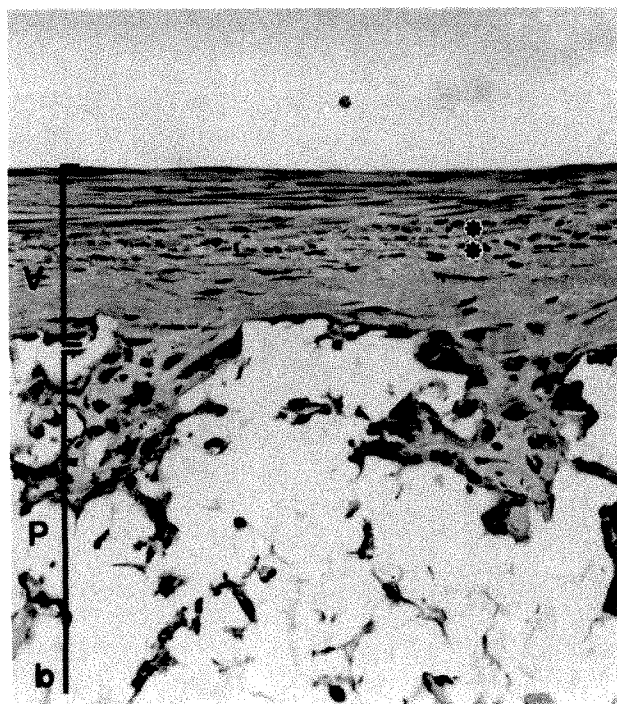
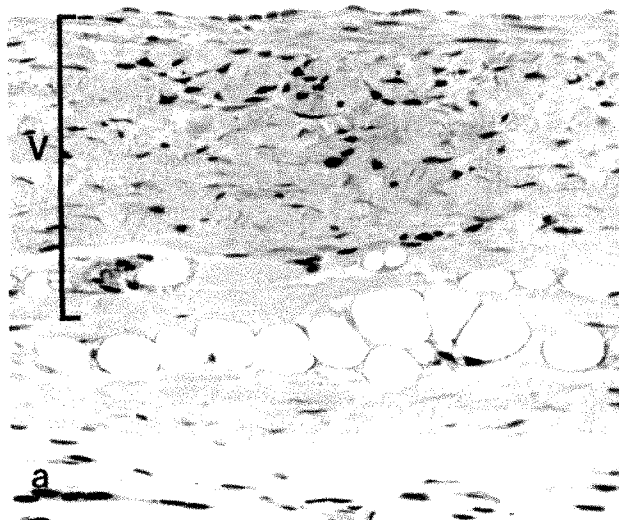


Fig 4. Light micrographs of (a) a control vein graft and (b) a composite vein graft 6 weeks after implantation. (a) Note the irregular orientation of fibrocytes in the control vein graft. (b) The vein wall of the composite vein graft has increased in thickness and shows several layers of circularly oriented, immature fibroblasts (*) underneath the regular, longitudinally oriented layers. (Hematoxylin and eosin; $\times 250$.) (P = prosthesis; V = vein wall.)

observed in our unsupported control vein grafts, and might therefore play an additional role in the development of degenerative changes in vein grafts.

In contrast, the composite vein grafts showed no complete disruption of the smooth muscle cell layers and only a minor inflammatory reaction on 1 day. Already after 1 week, the regular, longitudinally oriented layers of immature fibroblasts had regenerated, most likely from transformed preserved smooth muscle cell layers in the vein graft wall [4, 6]. This transformation into fibroblasts might be induced by ischemia resulting from the unavoidable interruption of vasa vasorum [6, 26]. The organized structure of the supported vein graft walls might be due to the preservation of its matrix function, as demonstrated by the preservation of elastic laminae. During the following weeks, the vein wall gradually increased in thickness by regular proliferation of fibroblasts, which in some areas had a prevalence for circular orientation. Elastic laminae were less pronounced at 6 weeks, probably because of elastase produced by macrophages [27] that were present in the chronic reaction against the prosthetic material. The fibroblasts remained immature and did not become mature, ie, fibrocytes, as in the unsupported vein grafts. Long-term studies are required to see if these immature fibroblasts will differentiate into myofibroblasts and myoblasts and will produce elastin, thus resulting in the formation of an arteriallike structure.

In conclusion, this study demonstrated that a compliant, biodegradable prosthesis can function as a protective scaffold for autologous vein grafts. The reduced damage is

especially expressed by a reduced infiltration of PMNs. Our rabbit model appeared to be very sensitive for evaluating damage to vein grafts, resulting in already great short-term consequences for the control vein grafts. Long-term studies are warranted to determine the ultimate role of the supporting prosthesis in terms of the function and biological behavior of autologous vein grafts implanted into the arterial system of rabbits.

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Safe Pulmonary Preservation for 12 Hours With Low-Potassium–Dextran Solution

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The function of porcine left lung allografts was studied after perfusion with (150 mL/kg) and storage for 12 hours in a 4° to 6°C low-potassium–dextran solution (Perfadex; Kabi Pharmacia AB, Uppsala, Sweden). After a left lung transplantation, an artificial lung in the form of venoarterial extracorporeal membrane oxygenation was established. The artificial lung has a “biological” heparin-coated surface (Carmeda AB, Stockholm, Sweden), and there is no need for systemic anticoagulation. Immediately thereafter, pneumonectomy of the normal right lung was done. All the animals were weaned from the artificial lung within 1 hour after the pneumonectomy.

Six animals were followed up for 24 hours. They were in good condition throughout the 24-hour observation period with arterial oxygen tensions around 200 mm Hg (inspired oxygen fraction = 0.4) and arterial carbon dioxide tensions around 40 mm Hg. This study demonstrates a reliable method for continuous evaluation of the function of a transplanted lung immediately after transplantation and over the ensuing postoperative period. Safe 12-hour lung preservation can be obtained with the low-potassium–dextran solution Perfadex.

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Numerous lung preservation studies have been carried out using many different models and techniques of assessment, but often with conflicting results [1, 2]. Simple cooling of the lung by immersion is satisfactory for up to 5.5 hours [3]. In the discussions during the Second International Seminar on Transplantation for End-Stage Lung Disease in Zürich, June 27 and 28, 1991, it became clear that most centers use modifications of Euro-Collins solution as the flush solution for clinical lung preservation. Euro-Collins solution has an intracellular electrolyte composition with a high content of potassium (115 mmol/L) and no colloids or other substances with high molecular weights.

It has been shown that Euro-Collins solution preserves lungs for up to 6 hours [4]. Fujimura and associates [5] have reported greatly prolonged lung preservation with an extracellular type of flush solution containing dextran. They did not objectively assess early lung function. This was done by Cooper's group [6], who showed significantly better immediate function of the lung preserved with a low-potassium–dextran solution compared with Euro-Collins solution. Their study demonstrates the difficulties in assessing a single transplanted lung if the contralateral normal lung is left in place. They point out that the failure to assess the function in the transplanted lung alone has contributed to the confusion regarding techniques for lung preservation over the past 20 years.

The most logical way to solve the problem of early assessment would be to do a double-lung transplantation

or a pneumonectomy of the normal nontransplanted lung immediately after the transplantation, thereby making the animal 100% dependent on the newly transplanted lung. However, such procedures are accompanied by a high operative mortality, especially if the function of the transplanted lung is less than perfect. Therefore, Cooper's group [6] introduced left and right pulmonary artery (PA) occlusion cuffs in a canine left lung allotransplant model. With this model, the right PA can be occluded, permitting measurements of blood gases and hemodynamic variables for short periods during which the whole right cardiac output goes through the transplanted lung. The drawback of such a model is that it can be used only for short periods, as prolonged total occlusion of the PA will destroy the lung [7]. In a porcine model, we [8] have shown that when about 25% of the cardiac output goes through the lungs at normothermia, the integrity of the lungs is disturbed, although their capacity to transfer oxygen and carbon dioxide is good.

The aim of the present study was to develop an adequate method for continuous evaluation of the function of a transplanted lung immediately after transplantation and during the postoperative period. “A lung preservation technique suitable for clinical transplantation must reliably provide excellent function immediately and over the ensuing postoperative period” [6]. The method presented here includes single-lung transplantation, establishment of an artificial lung, and immediately thereafter, pneumonectomy of the contralateral normal lung. To test the method, we used a low-potassium–dextran solution for 12-hour pulmonary preservation in left lung transplantation in pigs.

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Material and Methods

Fifteen Swedish native-breed pigs with a mean weight of 40 kg (range, 38 to 43 kg) were used (7 donors, 7 recipients, and 1 pig having a sham operation). All the animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH publication No. 85-23, revised 1985).

Donor Procedure

Anesthesia was induced with intramuscular administration of ketamine hydrochloride (Ketalar; Parke-Davis, Morris Plains, NJ), 30 mg/kg, and atropine sulfate, 1 mg. Sodium thiopental (Pentothal; Abbott Laboratories, North Chicago, IL), 5 to 8 mg/kg, was given intravenously before a tracheostomy (No. 7 tube) was done. Anesthesia and muscular relaxation were maintained with a continuous infusion of 40 mL/h of a mixture of 3 g of ketamine, 200 mg of pancuronium bromide (Pavulon; Organon Teknika, Bostel, the Netherlands), and 10 mg of midazolam hydrochloride (Dormicum; Roche, Basel, Switzerland) dissolved in 500 mL of 10% glucose. The animals were ventilated with a Siemens-Elema Servoventilator 900B. Air enriched with oxygen to an inspired oxygen fraction of 0.4, and fixed-volume ventilation of 8.5 L/min, 20 breaths/min, and a positive end-expiratory pressure of 5 cm H₂O was used.

A median sternotomy was performed. The incision was carried down into the abdomen, and the abdominal viscera were lifted away from the diaphragm to avoid compressing the lower lobes of the lungs. After systemic heparinization (500 U/kg), a 28F cannula 30 cm long was inserted into the PA. The infusion system consisted of a tube 240 cm long with an inner diameter of 11 mm connected to the 28F cannula in the PA. An arterial catheter was also inserted into the PA through a separate pursestring suture. This catheter was used for continuous monitoring of PA pressure by means of a transducer connected to a polygraph during perfusion of the lungs.

The left and right pleural spaces were entered. All parts of the lungs were carefully inspected, and the positive end-expiratory pressure was increased temporarily until all atelectasis was eliminated. A temperature probe was placed in the upper lobe of the right lung as far anteriorly as possible. A pursestring suture was placed in the left atrial appendage, and the free ends of the suture were pulled through a small tourniquet.

The superior and inferior caval veins and the ascending aorta were clamped. A small cut was made within the pursestring suture in the left atrial appendage. The PA was flushed with 6 L (150 mL/kg) of cold (4° to 6°C) Perfadex (Kabi Pharmacia AB) solution. Perfadex is commercially available. One thousand milliliters of Perfadex contains the following: dextran 40 (Kabi Pharmacia AB), 50 g; Na⁺, 138 mmol; K⁺, 6 mmol; Mg²⁺, 0.8 mmol; Cl⁻, 142 mmol; SO₄²⁻, 0.8 mmol; H₂PO₄⁻ + HPO₄²⁻, 0.8 mmol; glucose, 0.91 g; and hydrochloric acid and sodium hydroxide to pH 6 with sterile water in sufficient quantity. The mean perfusion pressure was adjusted to between 10

and 20 mm Hg by changing the level of the Perfadex container or by regulating the size of the hole in the left atrial appendage.

The duration of the flushing was 9 minutes in the first 2 donors. In the last 5 donors, the flow (by elevating the Perfadex container) and the size of the hole in the left atrial appendage were increased, and the flushing time was reduced to a mean of 3 minutes 13 seconds (range, 3.10 to 3.25 minutes). No topical cooling of the lungs was used. During the entire perfusion period, the lungs were fully ventilated as already described. After perfusion, the tracheal tube was disconnected from the ventilator, and the lungs were permitted to collapse.

The heart-lung block was carefully excised (10 minutes) and placed in a bowl containing Perfadex. With the heart-lung block floating in cold Perfadex, the left lung was carefully dissected from the block (20 minutes). A large atrial cuff was fashioned around the orifices of the left lung veins. The left main bronchus was divided near the carina and closed with a suture. The left lung was then placed in a glass container with cold (4° to 6°C) Perfadex, and was kept under the surface with a multiperforated perspex disc. A temperature probe was submerged in the container, which was placed in a refrigerator. During storage, the temperature was kept at 4°C and was recorded on a polygraph.

Recipient Procedure

On the following day, the recipient pig was sedated and anesthetized as described for the donor. The animal received 1.2 g of intramuscular benzylpenicillin procaine (Ilocillin; Ciba-Geigy, Basel, Switzerland). A tracheostomy was carried out and a No. 7 tracheal tube inserted. Two central venous catheters were introduced through the internal jugular vein. A catheter was placed in the aorta through the carotid artery. A Foley catheter was inserted into the urinary bladder through a suprapubic cystostomy.

A left thoracotomy through the sixth intercostal space was done and a left pneumonectomy performed, with care being taken to leave long stumps on the artery, veins, and bronchus. The left main bronchus was occluded near the carina with a Satinski vascular clamp. The bronchial anastomosis was performed first with a running suture of 4-0 Prolene (Ethicon, Somerville, NJ). A low dose of heparin sodium (100 U/kg) was then given. A gracile Satinski vascular clamp was placed intrapericardially across the lateral wall of the left atrium, incorporating the stumps of the three to four left pulmonary veins. Great care was taken to avoid occlusion of the coronary sinus or the venous return from the infracardiac lobe of the right lung.

An atrial cuff was then formed by an incision joining the superior and inferior pulmonary veins. The atrial anastomosis was performed with a running 5-0 Prolene everting suture. This suture was left untied. A vascular clamp was placed on the proximal PA, and the PA anastomosis was performed with a running suture of 5-0 Prolene, which was left untied as well. The Satinski clamp on the bronchus was removed and ventilation started. The PA clamp was taken off, and when blood filled up to the atrial

suture line, the clamp was removed from the left atrium. A catheter for the measurement of left atrial pressure was placed into the left atrium through the opening between the untied sutures, which were then tied.

A blood flow probe (14 mm) was placed around the left PA, and flow was continuously monitored on a Transonic flowmeter T201D (Transonic Systems Inc, Ithaca, NY). After some minutes of ventilation with a temporary increase in positive end-expiratory pressure from 5 to 10 cm H₂O, all atelectases disappeared. When blood flow through the transplanted lung reached a steady level, the PA suture was tied without stenosis. The thoracotomy was closed with the help of towel clips.

The artificial lung was then prepared [7, 8]. It consists of a nonocclusive roller pump (Stöckert Instrumente, Munich, Germany), a hypothermia machine (Gambro, Lund, Sweden), and a hollow-fiber membrane oxygenator (Maxima; Medtronic, Anaheim, CA) with its built-in heat exchanger. A collapsible balloon placed in a sensor (Carmeda AB, Stockholm, Sweden) is interposed in the venous line. In the event of decreased venous return, this unit controls the roller pump. All surfaces that come in contact with the blood are supplied with a Carmeda Bioactive Surface (Carmeda AB) [9]. The artificial lung was primed with 5% human albumin (980 mL).

A sternotomy was performed. The pericardium was opened over the right atrial appendage, and a 5-0 Prolene pursestring suture was placed in the appendage. The right iliac artery was cannulated with a 20F wire-reinforced cannula (Research Medical Inc, Midvale, UT), and venous return to the artificial lung was provided by inserting a 28F wire-reinforced cannula into the right atrium; both these cannulas had been supplied with the Carmeda Bioactive Surface.

Bypass was initiated without administration of systemic heparin (apart from the 100 U/kg given in connection with the left atrial suture). A blood to oxygen gas ratio of 1:1 was held in the membrane oxygenator. The pig was turned with the right thorax up, and a right anterior thoracotomy was performed through the eighth intercostal space, connecting this incision with the abdominal part of the sternotomy. In this way, the right part of the sternum together with the cranial part of the thoracic wall could be lifted away, providing very good access to the right lung. Pneumonectomy of the right lung was done. In the last 2 pigs, the pneumonectomy was greatly facilitated by using a TA 90 long stapler (United States Surgical Corp, Norwalk, CT).

The pig was then placed in a semilateral position with the left side (ie, the transplanted lung) up. The right external jugular vein was prepared, and a No. 7 Swan-Ganz catheter was placed in the PA. Tracheal suction was carried out, and the transplanted left lung was inspected to ascertain that no atelectasis was present (a temporary increase in positive end-expiratory pressure to 15 cm H₂O was used to eliminate all atelectasis). From this point to the end of the experiment, the ventilator was fixed on a minute volume of 8.5 L with 20 breaths/min and 5 cm H₂O of positive end-expiratory pressure. From this moment, flow through the artificial lung was decreased gradually,

with particular attention paid to the central hemodynamics.

The fluid supply during the 24-hour experimental period was kept constant for all the animals and consisted of 960 mL of 10% glucose (ie, the anesthetic infusion of 40 mL/h), the 980 mL of 5% human albumin used as a priming solution (ie, after the artificial lung had been taken away, the blood in the circuit was given back), and 500 mL of 5% human albumin given as a continuous infusion during the last 12 hours of the experiment. No drugs were given during the experiment (except the anesthetics).

When blood flow had been established through the transplanted lung, the time was defined as zero. Blood gases (ABL 30; Radiometer, Copenhagen, Denmark) and oxygen saturation (OSM 3, adjusted for the pig mode; Radiometer), hemodynamics (all blood pressures were continuously displayed on monitors: Hewlett-Packard models HP78353B and HP78342B), lung compliance, urine volume, hemoglobin level, and hematocrit were registered every 4 hours throughout the experiment.

In the last pig in the study, a sham operation was done. A left thoracotomy and dissection of the left PA were carried out, and the flow probe was placed in the same position as if the lung had been transplanted. Everything else was performed in the same way as the recipient operations except that no artificial lung was used in connection with the right pneumonectomy.

Results

The mean ischemic time for the transplanted lungs was 12.75 hours (range, 12.5 to 13.5 hours). A typical polygraph registration of the donor procedure is shown in Figure 1. The lung temperature decreased to about 10°C (range, 8° to 14°C). Within 2 minutes after the end of perfusion, before the heart-lung block had been excised, the lung temperature increased to about 20°C and stayed there during the dissection (no topical cooling was used).

The mean time for the use of the venoarterial extracorporeal membrane oxygenator (ECMO) was 2 hours 20 minutes (range, 2 to 3 hours). A blood flow through the ECMO of up to 4 L/min could easily be obtained, but only 1.5 to 2 L/min was necessary to keep the central hemodynamics within normal limits during the right pneumonectomy. All the animals were weaned from the ECMO without difficulty within 1 hour after the right pneumonectomy had been done.

In pig 6, no urine production was seen although the central hemodynamics were within acceptable limits; acidosis was present (base excess, -12), and the oxygen saturation of mixed venous blood was very low (16%). The arterial blood gas measurements at 8 hours were as follows: oxygen tension, 92 mm Hg; carbon dioxide tension, 50 mm Hg; and oxygen saturation, 99%. There was still no urine production, and the experiment was terminated.

Minor variations were seen in blood gases and oxygen saturation throughout the 24 hours after transplantation (Fig 2). The compliance of the transplanted lungs was

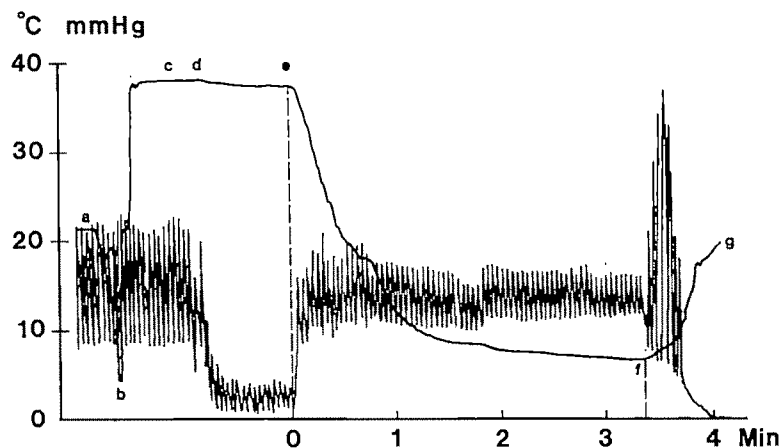


Fig 1. Typical polygraph registration of the donor procedure showing pulmonary artery pressure (thin line) and temperature in the anterior segment of the superior lobe of the right lung (thick line). Ventilation with 20 breaths/min causes the fluctuations in the pulmonary artery pressure curve. (a = room temperature; b = temperature of Perfadex solution; c = lung temperature; d = clamping of caval veins; e = start of perfusion with 6 L of Perfadex solution; f = end of perfusion; g = lung temperature 45 seconds after perfusion.)

reduced after 4 hours of reperfusion but did not decrease further during the next 20 hours (Fig 3). The cardiac output, blood pressures, and urinary output were stable throughout the observation time (Fig 4) with only minor variations in systemic and pulmonary vascular resistances (Fig 5). The blood was diluted by the priming solution in the ECMO system to a hematocrit of 0.25 to 0.30 (Fig 6). There was no need for blood transfusions, diuretics, or other drugs.

The results obtained in the pig having a sham operation are shown in the figures as triangles connected by a broken line. Because no ECMO was used in this pig, it was not hemodiluted by the priming solution and its hematocrit was higher (see Fig 6). Moreover, as it did not get the priming solution of 980 mL of 5% albumin, its blood volume was less and its vascular resistance, greater (see Fig 5).

Comment

The use of venoarterial extracorporeal membrane oxygenation during the pneumonectomy of the contralateral normal lung made the operation safe without negative incidents of any kind. The ECMO system gives the opportunity to measure the function of the transplanted lung immediately and decide when it is possible to divert all venous return through the lung. With the knowledge of the blood flow through the ECMO system (ie, read from the calibrated roller-pump flow meter), cardiac output of the pig (ie, the flow through the transplanted lung), blood gases, oxygen saturation, and hemoglobin before and after passage through the artificial or transplanted lung, calculations of the oxygen delivery can be done and monitored continuously. The consequence of different perfusion pressures or flows in the transplanted lung can be investigated by regulating the flow through the artificial lung. If the transplanted lung has impaired function at the beginning, the time of extracorporeal membrane oxygenation can be prolonged as long as needed, as no anticoagulation is required and no major destruction of the blood occurs in healthy pigs. Our experimental and clinical experience with this novel artificial lung with the

"biological" Carmeda surface has recently been published [7, 8, 10-13]. Because all the transplanted lungs in this study had excellent early function, all the animals could be weaned from the ECMO after the pneumonectomy of the contralateral lung.

One animal in this study (pig 6) did not complete the whole observation period of 24 hours. No urine production was seen during the first 8 hours of observation. Transplantation, establishment of extracorporeal membrane oxygenation, and weaning from the artificial lung were performed without problems; the arterial blood gases and oxygen saturation were within acceptable limits. Therefore it is not probable that the anuria was caused by poor pulmonary preservation. The metabolic acidosis and the low mixed venous oxygen saturation measured in the pig suggest inadequate peripheral circulation as the cause of the anuria, although the hemoglobin level, aortic pressure, and cardiac output were not especially low. The study protocol did not allow any diuretics or other drugs to be given, and therefore that experiment was terminated.

A low-potassium-dextran solution has been shown to give better immediate lung function than Euro-Collins solution [6]. We [14] have shown that the high potassium content in Euro-Collins solution leads to strong pulmonary vasoconstriction, which is not significantly altered by prostaglandin E_1 . However, if the temperature in the PA is lower than 10°C, high potassium concentrations do not induce vasoconstriction [14]. A solution with no potassium or a low (ie, extracellular) concentration of potassium has an advantage over a high-potassium solution in that no vasoconstriction is induced. Vasoconstriction may cause impaired perfusion through more or less vasoconstricted regions of the lung. This situation creates a risk of underperfused or nonperfused regions with possible poor lung function after prolonged (ie, longer than 6 hours) storage.

What is thought to be the rationale for using a high potassium concentration in solutions for organ preservation? The basic hypothesis of Collins and Halasz [15] was that cation exchange across the cell membrane might be detrimental and can be avoided by flushing the organ

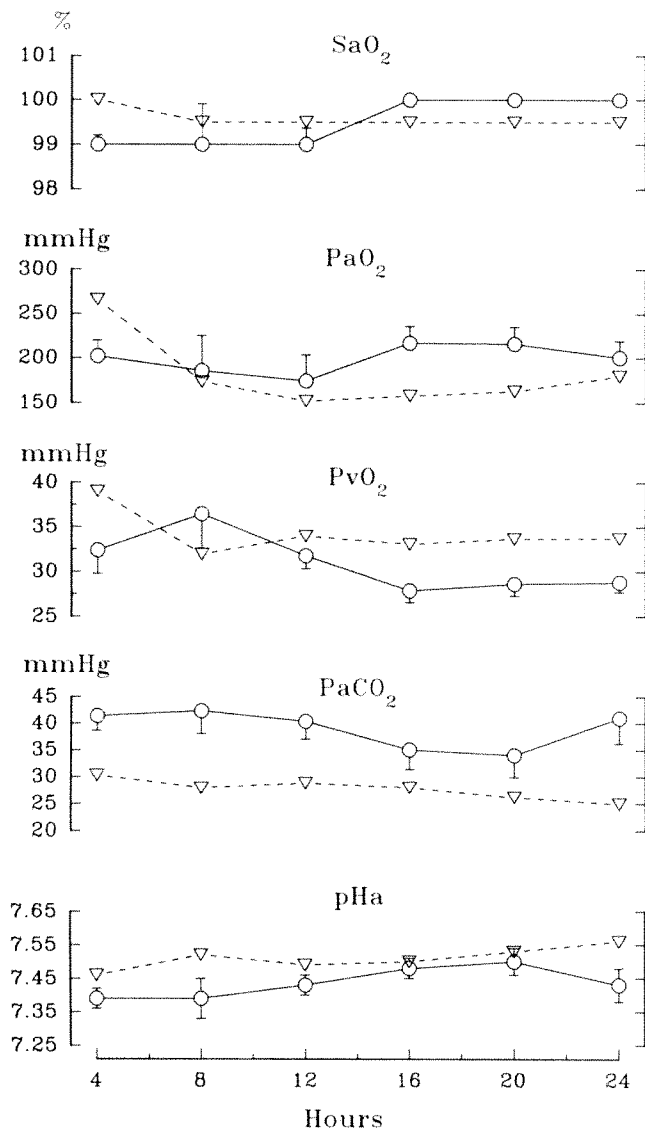


Fig 2. Function of transplanted left lung during the first 24 hours of reperfusion. Inspired oxygen fraction was 0.4. Arterial oxygen saturation (SaO₂), arterial oxygen tension (PaO₂), arterial carbon dioxide tension (PaCO₂), pH in arterial blood (pHa), and oxygen tension in mixed venous blood (PvO₂) from the pulmonary artery are shown as the mean $\pm$ the standard error of the mean (circles with uninterrupted line) ($n = 6$). The data for the pig having a sham operation are also shown (triangles with interrupted line).

with "intracellular" perfusate before anoxic hypothermic storage. This might save high-energy phosphate levels by decreasing the load on the sodium pump. To our knowledge, no studies have been published that demonstrate the advantages of high-potassium solutions in lung preservation.

More recently, attention has been focused on the content of cell membrane-impermeable solutes in organ preservation solutions. The maintenance of normal cell volume is an energy-requiring process and depends on the action of the cell membrane-bound Na-K adenosine triphosphatase. Sodium ions are actively pumped out of

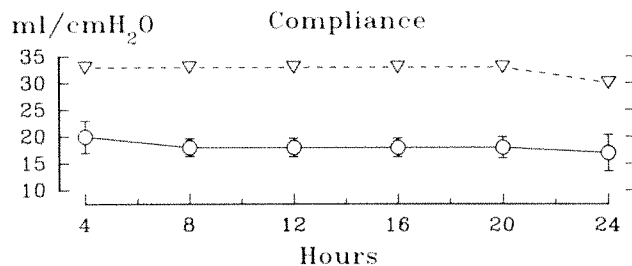


Fig 3. Lung compliance (closed chest) of the transplanted left lung during the first 24 hours of reperfusion. Lung compliance was defined as $V_T/P_{\text{pause}} - PEEP$, where V_T = tidal volume, P_{pause} = airway pressure at the end of inspiratory pause, and PEEP = positive end-expiratory pressure. Data are shown as the mean $\pm$ the standard error of the mean (circles with uninterrupted line) ($n = 6$). The data for the pig having a sham operation are also shown (triangles with interrupted line).

the cell, and this creates an osmotic effect, balancing that of the cell membrane-impermeable intracellular anions, mainly proteins [16]. Ischemia, which is a consequence of most organ preservation methods commonly in use, will create a lack of adenosine triphosphate, which is needed

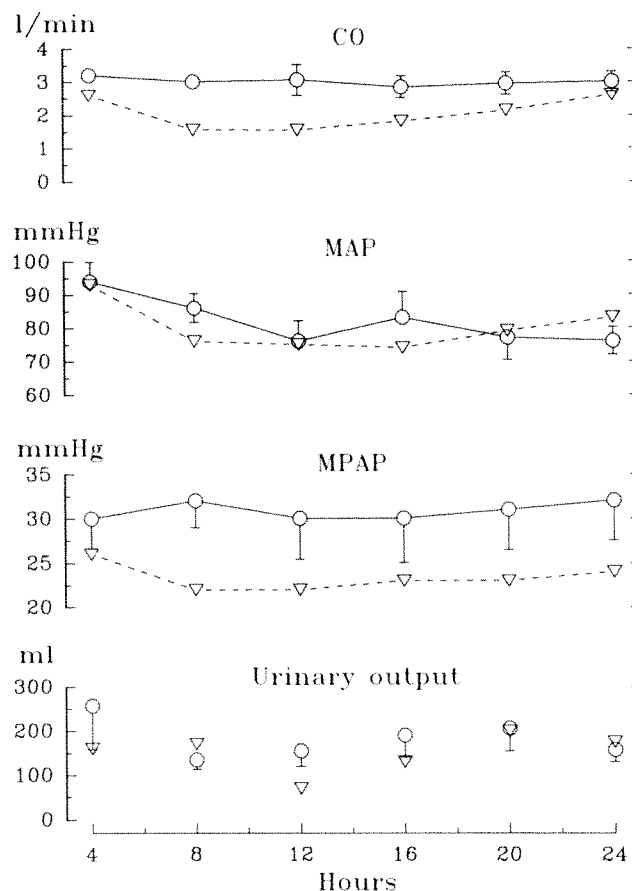


Fig 4. Hemodynamics and urinary output during the first 24 hours of reperfusion. Data are shown as the mean $\pm$ the standard error of the mean (circles with uninterrupted line) ($n = 6$). The data for the pig having a sham operation are also shown (triangles with interrupted line). (CO = cardiac output; MAP = mean arterial pressure; MPAP = mean pulmonary artery pressure.)

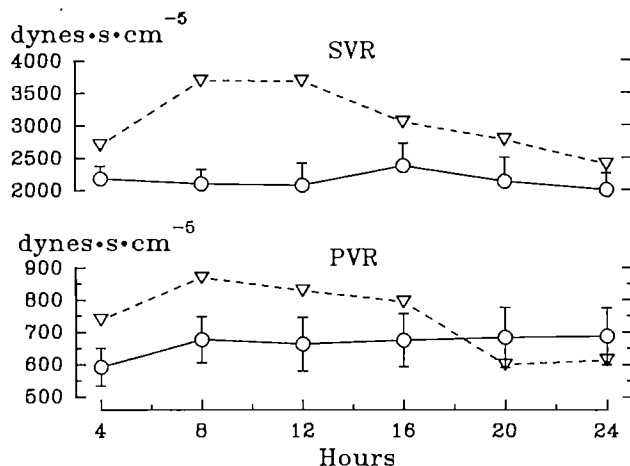


Fig 5. Systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) during the first 24 hours of reperfusion. Data are shown as the mean $\pm$ the standard error of the mean (circles with uninterrupted line) ($n = 6$). The data for the pig having a sham operation are also shown (triangles with interrupted line).

to give energy to the sodium pump. When the efficiency of this pump is reduced, sodium ions and water enter the cell and cause swelling of the cell and its organelles [17, 18]. Hypothermia, which is the mainstay of most organ preservation methods, inhibits Na-K adenosine triphosphatase, and the sodium pump becomes ineffective. Then cell swelling will occur even if sufficient levels of adenosine triphosphate are present [19]. It has also been shown that a difference in the cold sensitivity of the membrane pumps exists between different tissues; for example, the hypothermia-induced cell swelling is more prominent in the heart and liver than in the kidney [20].

The potential advantage of the addition of dextran to organ preservation solutions is that it is impermeable to cell membranes and therefore counteracts the obligatory

cell swelling caused by anoxic hypothermic storage. Glucose is an important solute in Collins solution. It has been shown to be relatively impermeable to kidney cell membranes; an adequate concentration of glucose will therefore balance the osmotic pressure of the kidney cell during ischemia/hypothermia, thus counteracting the cell swelling. This, rather than the high potassium content, is probably the explanation for the success of Collins solution in kidney preservation [21-24]. Collins solution is not able to counteract cell swelling in liver preservation because glucose is not impermeable to liver cell membranes; when solutes impermeable to liver cell membranes were added to liver preservation solutions, a breakthrough was obtained and safe preservation of the liver for 24 to 48 hours could be demonstrated [25]. To decide the adequate concentration of dextran in preservation solutions, further studies need to be done; the lower the temperature or the more cold sensitive the membrane pump in the particular organ, the higher the concentration of cell membrane-impermeable solute (eg, dextran) required to counteract the cell swelling.

Regardless of the type of organ preservation solution, an absolute prerequisite for successful long-term preservation of the lung is that the solution in question reaches all cells of the lung. We have observed that atelectatic parts of a lung will not be adequately perfused. It is therefore of the utmost importance that all parts of the lung be inspected before starting perfusion; if atelectasis is present, the ventilation must be increased temporarily until no signs of atelectasis can be seen. During perfusion, there must be enough ventilation to completely counteract the occurrence of atelectasis. We do not think that topical cooling during perfusion is essential; on the contrary, it might be harmful if its performance results in atelectasis.

Furthermore, deep hypothermia causes rigidity in the cell membranes [26], which will make them more vulnerable during dissection. In the present study, no topical cooling was used. The temperature in the lung during perfusion fell to about 10°C. Within 1 minute after completion of perfusion, the temperature became stable at around 20°C. The left lung was dissected ready for implantation at that temperature and then submerged in the 4°C low-potassium-dextran solution in an atelectatic state. Within 45 minutes, the temperature was 4°C in all lung regions (measurements done in the right lung).

We think it is essential that the perfusion pressure is adequate, ie, so high that it overcomes gravity and reaches the most anterior parts of the lung. In this study, the mean PA pressure was kept between 10 and 20 mm Hg during perfusion, and this effectively decreased the temperature in the most anterior parts of the lung, suggesting that these parts were perfused. If the hole made in the left atrial appendage is too large, the perfusion pressure can easily be too low unless the capacity of the infusion system used to deliver the preservation solution into the PA is high. The surgeon who is to harvest the heart most probably wants a large hole in the left atrium to decompress the heart fully. In an adult, high-flow perfusion will be needed to reach an adequate

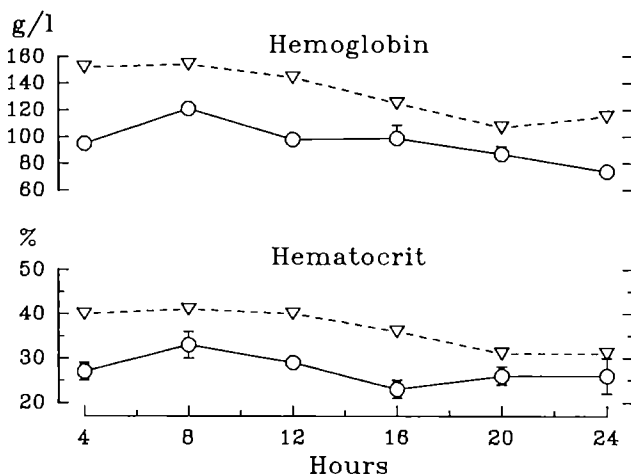


Fig 6. Hemoglobin and hematocrit during the first 24 hours of reperfusion. Data are shown as the mean $\pm$ the standard error of the mean (circles with uninterrupted line) ($n = 6$). The data for the pig having a sham operation are also shown (triangles with interrupted line).

perfusion pressure for all parts of the lung. Most commercial infusion systems we have seen do not have that high-flow capacity.

In conclusion, this study presents a reliable method to examine the function in newly transplanted lungs. The low-potassium-dextran solution Perfadex provides good preservation of lungs for 12 hours.

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Early Cardiac Allograft Rejection Is Independent of Regional Myocardial Blood Flow

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Noninvasive telemetric monitoring of canine heterotopic cardiac allograft unipolar peak-to-peak amplitude (UPPA) has permitted prospective surveillance for rejection; moreover, this technique is able to reliably detect rejection before the development of histologic evidence of myocyte necrosis. This study was performed to determine whether early cardiac allograft rejection and the accompanying decline in allograft UPPA were associated with alterations in regional myocardial blood flow (RMBF). Seven heterotopic, intrathoracic canine cardiac transplantations were performed using triple-drug immunosuppression. Native hearts and allografts were instrumented with right ventricular and left ventricular epicardial screw-in electrodes connected to subcutaneous telemeters. Daily measurement of native and graft UPPA was performed; using radioactive microspheres, native and graft RMBF were determined during the control period and when UPPA had declined by 15%, 30%, and 45%. Graft histologic status was determined by endomyo-

cardial biopsy at the time of RMBF determination. Mean duration of the study was 19.7 ± 3.9 days. Rejection was documented in all animals. The UPPA was stable in native hearts; UPPA declined in the allografts after the onset of rejection. A biphasic change in allograft blood flow was seen. Initially RMBF increased as UPPA declined; a 30% to 45% reduction in UPPA was associated with a 41% increase in RMBF ($p = 0.028$ versus allograft control). Subsequently, a significant decline in blood flow was observed for reductions in UPPA greater than 45% (0.68 ± 0.44 versus $1.07 \pm 0.47 \text{ mL} \cdot \text{g}^{-1} \cdot \text{min}^{-1}$ for a 30% to 45% decline in UPPA; $p = 0.007$). The results of this study indicate that the initial stage of cardiac allograft rejection is not associated with a decline in RMBF. Moreover, the fall in UPPA that occurs with early rejection must be due to electrophysiologic factors that are independent of RMBF.

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The peak-to-peak amplitude of the unipolar intramyocardial electrogram (UPPA) has been shown to be sensitive to a variety of alterations in myocardial physiology. The UPPA falls rapidly after the onset of acute regional ischemia in canine ventricular myocardium [1], and acute changes in ventricular volume have been shown to result in inverse changes in UPPA [2, 3]. In both animals and humans a decline in UPPA occurs during rejection in cardiac allografts [4-7]. This decline coincides with the development of mild histologic rejection and progresses linearly with increasing severity of rejection [5, 6]. The relationship between the degree of UPPA decline and the severity of rejection is unaffected by the presence of maintenance immunosuppression [6]. In addition UPPA has been shown to remain stable in histologically quiescent myocardium both acutely [6, 8] and chronically [8]. All of these characteristics suggest that the decline in UPPA is a specific electrophysiologic response to the cellular or humoral events occurring during cardiac allograft rejection. However, the mechanism of UPPA decline during acute allograft rejection is unknown.

One of the earliest histologic changes that occurs during rejection is a mononuclear perivascular infiltrate [9], and it has been suggested that alterations in regional myocardial blood flow (RMBF) may accompany the rejection process. The left ventricular (LV) RMBF in orthotopic cardiac allografts has been shown to decline during severe unmodified rejection [10-12]. However, the changes in RMBF during early rejection in the presence of cyclosporin A (CSA)-based immunosuppression are unknown. The present study was performed to determine if the initial rejection that occurs through CSA-based immunosuppression, and is accompanied by a decline in UPPA, is associated with alterations in RMBF.

Material and Methods

Experimental Preparation

Intrathoracic heterotopic cardiac transplantation was carried out as previously described [6]; briefly, donor hearts were obtained after cardioplegic arrest and implanted into the left chest of recipient animals with aorta-to-brachiocephalic and pulmonary artery-to-superior vena cava anastomoses. Before implantation a graft atrial septal defect was created by blunt disruption of the fossa ovalis.

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During graft preparation, two unipolar epicardial electrodes were placed in midwall positions on the right ventricle and left ventricle of the native heart (Pacesetter Systems, Inc, Sylmar, CA), and an indwelling left atrial catheter was placed in the native heart for use in RMBF determinations. After implantation, the graft was deaired, reperfused, and cardioverted to normal sinus rhythm. After a 20- to 30-minute recovery period, two unipolar intramyocardial screw-in electrodes were placed in mid-wall positions on the allograft right and left ventricles (Pacesetter Systems, Inc). Care was taken to ensure that no evidence of regional hypoperfusion was present after electrode placement. The native heart electrodes and graft electrodes were connected to separate subcutaneously implanted telemetric pacemakers. Finally, a radiopaque tape was placed around the graft pulmonary artery near the anastomosis, the native left atrial catheter was positioned subcutaneously beneath the dorsal soft tissue, and the thoracotomy was closed. All animals were allowed to recover undisturbed for 5 days. Animals received humane care in compliance with the principles of laboratory animal care formulated by the National Society for Medical Research and the "Guide for the Care and Use of Laboratory Animals" prepared by the National Academy of Sciences and published by the National Institutes of Health (NIH publication No. 85-23, revised 1985).

Immunosuppression Protocol

Recipients were given CSA (15 mg/kg) and methylprednisolone (500 mg intravenous bolus) preoperatively. Postoperatively, maintenance immunosuppression consisted of CSA (15 mg · kg⁻¹ · day⁻¹), prednisone (10 mg/day) and azathioprine (1.5 mg · kg⁻¹ · day⁻¹). If no evidence of rejection was present by postoperative day 18, azathioprine administration was discontinued and the daily CSA and prednisone dose was reduced by 50%.

Data Acquisition and Analysis

ELECTROGRAMS. Unipolar electrograms from each intramyocardial electrode were obtained by noninvasive telemetry (AFP Pulse Generator/Telemeter model 825; Pacesetter Systems Inc). The telemetered analog FM signal was acquired by a modified APS I programmer (model 370; Pacesetter Systems Inc [5]), digitized at 1,000 Hz, and subsequently displayed in real time (25 mm/s). Beginning on postoperative day 6, electrograms were recorded during sinus rhythm daily from each lead. All interrogations were performed with the animal awake and resting quietly. No attempt was made to schedule the acquisition of electrophysiologic data with respect to time of day.

The UPPA (in millivolts) was measured for all electrograms recorded during each interrogation, and a mean UPPA value was calculated for each lead. For both native hearts and allografts the daily UPPA was calculated as the sum of the mean UPPAs for the RV and LV electrodes. The control UPPA for both the native heart and allograft was then calculated as the respective mean daily UPPA over postoperative days 6 through 10 (control period). The daily UPPA for both the native heart and allograft was then normalized as percentage of the respective

control UPPA. A normalized daily UPPA of less than 85% control was considered positive for rejection and was used as an indication for RMBF determination and endomyocardial biopsy (EMB). Further reductions in UPPA to less than 70% and less than 55% of control were indications for subsequent RMBF determinations and EMBs.

REGIONAL MYOCARDIAL BLOOD FLOW DETERMINATION. All RMBF determinations were performed after anesthetic induction and ventilation and before EMB. Determinations of RMBF were performed using radioactive microspheres (14 μm diameter; 10% dextran suspension; Medical Products Division, 3M, St. Paul, MN) tagged with one of the following isotopes: cerium 141, chromium 51, niobium 95, scandium 46, or strontium 85. Before each determination microspheres were thoroughly mixed and then rapidly injected through the left atrial line (≈8.7 × 10⁶ microspheres/injection). Reference blood samples were withdrawn from the femoral artery using a withdrawal pump (Harvard Apparatus, South Natick, NJ) at 7.5 mL/min, beginning 15 seconds before microsphere injection and continuing for 2 minutes after injection.

At sacrifice the excised native and grafted hearts were prepared for counting by removal of atrial, pulmonary arterial, aortic, and valvular tissue and stripping of large epicardial arteries and veins. The RV and LV myocardium were then divided into 60 (20 RV, 20 LV endocardial [ENDO], and 20 LV epicardial [EPI]) tissue samples. These samples were weighed and counted for radionuclide activity. Raw counts were obtained using a gamma well counter (Packard Auto-Gamma 5000, Packard Instrument Co, Meriden, CT) and then corrected for background, decay, and spillover (Compusphere, Packard Instrument Co) to obtain final activity (CTS_{corr}). Regional myocardial blood flow (mL · g⁻¹ · min⁻¹) was calculated as:

$$\text{RMBF} = \left(\frac{\text{Sample CTS}_{\text{corr}}}{\text{Reference blood sample CTS}_{\text{corr}}} \right) \cdot \left(\frac{7.5 \text{ mL/min}}{\text{Sample wt (g)}} \right)$$

ENDOMYOCARDIAL BIOPSIES. Endomyocardial biopsy specimens were obtained as previously described [5]. A minimum of six tissue fragments were obtained at each biopsy session. These samples were prepared for histologic grading by formalin fixation and hematoxylin and eosin staining. Biopsy specimens were evaluated for the adequacy of sampling and presence or absence of rejection by a single pathologist blinded to the study design. Qualitative histologic grading classified rejection in each biopsy as none, mild, moderate, or severe [9]. Mild rejection was characterized by perivascular (or focal interstitial) lymphocytic infiltrates. Moderate rejection involved more extensive interstitial inflammation without myocyte necrosis. The presence of marked interstitial inflammation and myocyte necrosis characterized severe rejection.

Although the degree of rejection may vary among the tissue fragments obtained in any given biopsy [9], a single qualitative grade of rejection is usually assigned. To

quantify rejection in a manner that would reflect the intermediate degrees of rejection in biopsy specimens containing tissue fragments with various degrees of rejection, the following methodology was developed: the tissue fragments in each specimen were divided into two samples, A and B, composed of n_A and n_B tissue fragments, respectively. A single qualitative grade was then given to each sample, with a corresponding numeric value, k , assigned to each grade (none = 0, mild = 1, moderate = 2, severe = 3). A rejection score (RS) was then calculated for each biopsy specimen as follows [5, 6]:

$$RS = \frac{[(k_A \cdot n_A) + (k_B \cdot n_B)]}{(n_A + n_B)}$$

Rejection was present by histologic criteria for any biopsy specimen with an RS greater than 0.66. In using this methodology biopsy specimens in which two thirds or more of the fragments were graded as showing mild rejection and any specimen with a sample graded as showing moderate or severe rejection would have a calculated RS greater than 0.66. After the final EMB (ie, that EMB directed by the reduction in UPPA to less than 55% control) animals were sacrificed by anesthetic overdose (pentothal, 10 mg/kg) and intravenous potassium chloride.

HEMODYNAMICS. In 6 of the 7 animals, hemodynamic data were acquired immediately before termination of the study. After the final RMBF determination and EMB, the graft was reexposed through the original left thoracotomy and carefully dissected from the surrounding adhesions. Once the graft was mobilized the RV and LV systolic and diastolic pressures were obtained by transduction of a fluid-filled catheter inserted through the apices of the graft. Simultaneous recipient femoral artery pressures were obtained. After pressure recording, a large stent (5 mm diameter, 4 cm length) was inserted into the LV apex and a timed blood collection performed.

STATISTICAL ANALYSIS. Statistical comparisons of rejection score were made using an analysis of variance program (ANOVA; SYSTAT, Evanston, IL). Analyses of RMBF were performed using a three-factor ANOVA (SAS Inc, Cary, NC). Analysis of residual error terms resulting from ANOVA performed using the absolute values of blood flow measured for each heart indicated that the error terms resulting from the analysis could not satisfy the required tests of independence and normal distribution. Accordingly, a logarithmic transformation was performed on the blood flow data, and subsequent application of ANOVA resulted in residuals that satisfied the testing criteria. The logarithmic transformation was performed because of the greater power, interpretability, and control of experimentwise error rate available with ANOVA as compared with that available with nonparametric techniques. Type III sums of squares were performed to check for significant interaction effects between the factors ORGAN (native or graft heart) and UPPA (the four UPPA ranges used to direct RMBF measurements), and SITE

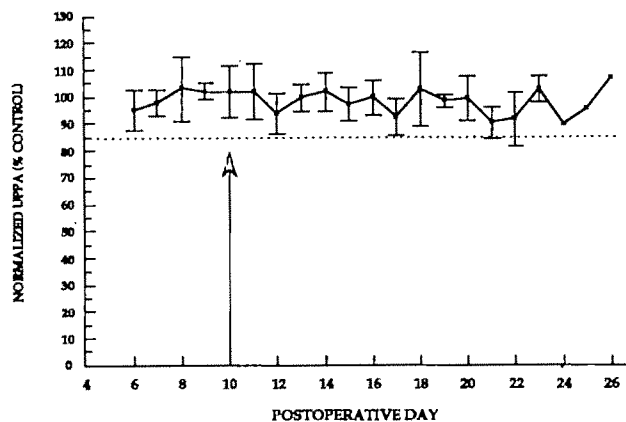


Fig 1. Mean ($\pm$ standard deviation) daily unipolar peak-to-peak amplitude (UPPA) for the native hearts in the study group. The arrow indicates the last day of the control period (postoperative days 6 through 10). Only 1 animal survived more than 23 days postoperatively.

(the RV, LV EPI, or LV ENDO regions). Based on the results of these factor analyses, subsequent analyses of treatment means were performed. Where appropriate, the p values reported have been corrected using Bonferroni procedures. Hemodynamic comparisons were made using Student's t test. In all statistical analyses significance was assigned for p values less than 0.05. All data are expressed as mean $\pm$ standard deviation.

Results

Seven heterotopic transplantations were performed. The mean duration of the study was 19.7 ± 3.9 days. Rejection was documented (both electrophysiologically and histologically) in all animals; in 2 animals histologic rejection was documented during the control period, and in 3 other animals rejection occurred through full immunosuppression. In the remaining 2 animals rejection was documented only after immunosuppression was reduced by 50%. At postmortem examination there was evidence of significant regional inflammation, including the presence of pleural effusions in all animals and, in several cases, native heart pericardial effusions.

Unipolar Peak-to-Peak Amplitude

Figure 1 shows the mean daily UPPA telemetrically recorded from native hearts on each postoperative day for the group. Analysis revealed a high degree of native heart UPPA stability over the 103 experimental days. In 101 of 103 determinations (98%) the normalized UPPA was greater than 85%. In 2 animals, the normalized UPPA was less than 85% on one occasion. One of these occurred during the control period (normalized UPPA = 82.4%) and one occurred immediately after the control period (normalized UPPA = 83.5%). None of these occurred after a reduction of immunosuppression. In 1 animal (normalized UPPA = 83.5%) the reduction in UPPA occurred in the presence of mild to moderate rejection in the graft. However, in that animal UPPA returned to levels greater than 85% control on the following day and remained

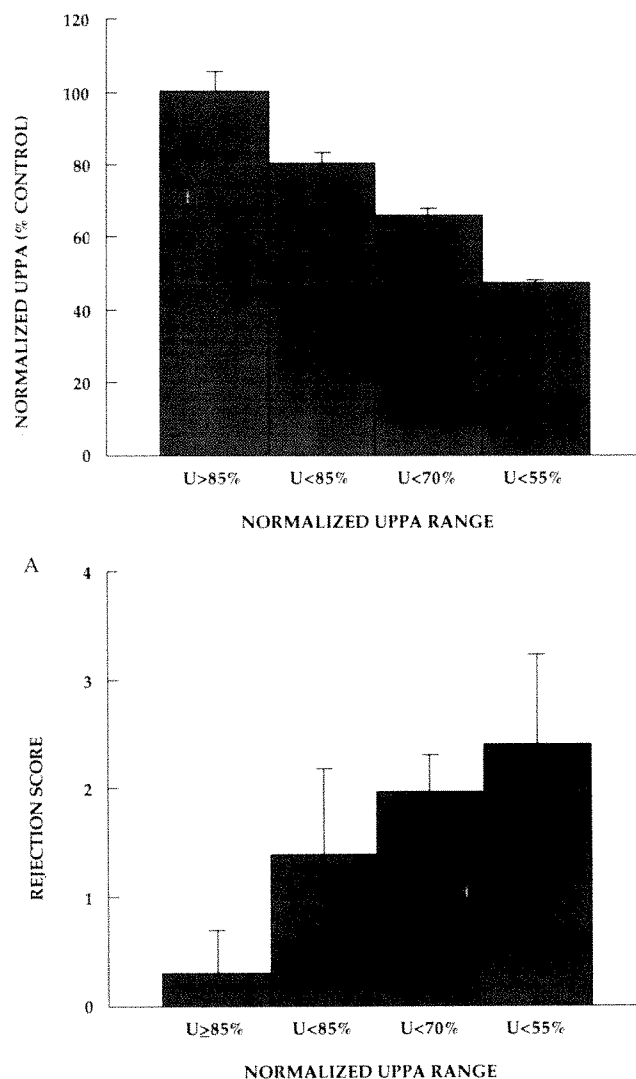
above that level even in the presence of subsequent severe graft rejection.

Seven baseline EMBs were performed (one in each animal); six of these were negative for rejection. In 1 animal the initial control biopsy specimen was associated with mild rejection (normalized UPPA = 96.5%; RS = 1.0). After the control period 20 UPPA-directed EMBs were performed; three of 20 were prompted by persistent UPPA stability (normalized UPPA $\geq$ 85%) during postoperative days 11 through 16, and 17 of 20 were due to a reduction in UPPA to less than 85% (6 EMBs; mean RS = 1.38 ± 0.80), less than 70% (5 EMBs; mean RS = 1.96 ± 0.35), or less than 55% (6 EMBs; mean RS = 2.41 ± 0.82) control. In specimens from one of the three biopsies directed by UPPA stability during the first week after control, mild rejection was noted (normalized UPPA = 92.7%; RS = 1.0). Among the 17 biopsies directed by a decline in UPPA, one showed no rejection (normalized UPPA = 80.5%; RS = 0) and 16 showed rejection. Successive declines in UPPA correlated with increasing severity of rejection ($p < 0.001$). Figure 2 shows the mean normalized UPPA and the mean RS calculated for each normalized UPPA range.

Regional Myocardial Blood Flow

Figure 3 shows the mean control and overall RMBF by organ and site. Type III sums of squares for the interactions of ORGAN and UPPA, SITE and UPPA, and ORGAN, SITE, and UPPA revealed no significant differences (p values = 0.483, 0.999, and 0.952, respectively). A significant difference was noted for ORGAN and SITE ($p = 0.017$). Accordingly, subsequent analyses of mean RMBF for various sites in both native and graft hearts were performed. Overall native RV RMBF was significantly lower than LV RMBF (0.76 ± 0.41 versus 1.36 ± 0.55 mL $\cdot$ g $^{-1}$ $\cdot$ min $^{-1}$; $p = 0.001$). No difference was seen between native LV ENDO and EPI RMBF ($p = 0.356$). Native LV RMBF was significantly greater than the graft LV RMBF (1.36 ± 0.55 versus 0.82 ± 0.45 mL $\cdot$ g $^{-1}$ $\cdot$ min $^{-1}$; $p = 0.001$). No difference was seen between native and graft RV RMBF (0.77 ± 0.41 versus 0.78 ± 0.51 mL $\cdot$ g $^{-1}$ $\cdot$ min $^{-1}$; $p = 0.959$); however, RMBF was greater in native LV ENDO and EPI regions than in corresponding regions of the grafted hearts (1.45 ± 0.56 versus 0.89 ± 0.41 mL $\cdot$ g $^{-1}$ $\cdot$ min $^{-1}$ for ENDO and 1.28 ± 0.55 versus 0.79 ± 0.44 mL $\cdot$ g $^{-1}$ $\cdot$ min $^{-1}$ for EPI; $p = 0.001$ for both comparisons). Within the grafted hearts no differences were seen between RV, LV ENDO, and LV EPI RMBF ($p = 0.315$ for RV versus LV total, and $p = 0.333$ for LV EPI versus LV ENDO).

Figure 4 shows the mean RMBF by organ, site, and normalized UPPA range. Analysis of variance revealed a significant difference in RMBF in both native and graft hearts when blood flow was referenced to graft UPPA level. Overall RMBF declined in native hearts as graft UPPA declined ($p = 0.001$); however, this difference emerged only after the graft UPPA had fallen to less than 55% ($p = 0.005$). No decline in native RMBF was associated with the observed decline in native RMBF. Native RV, LV ENDO, and LV EPI RMBF when graft UPPA was



B

Fig 2. (A) The mean normalized unipolar peak-to-peak amplitude (UPPA) for each range of UPPA values (U) that determined the timing of regional myocardial blood flow determinations and endomyocardial biopsies. Normalized UPPA less than 85% was considered indicative of rejection. (B) Mean rejection score calculated for endomyocardial biopsy specimens obtained for each range of normalized UPPA values. A calculated rejection score of 0.66 or greater was considered positive for rejection.

less than 55% were 0.45 ± 0.16 , 1.07 ± 0.35 , and 0.83 ± 0.25 mL $\cdot$ g $^{-1}$ $\cdot$ min $^{-1}$, respectively. No change in native RMBF was noted for reductions in normalized graft UPPA of 15% to 30% or 30% to 45% ($p > 0.631$).

In contrast, a biphasic relationship between graft RMBF and normalized graft UPPA was noted. Initially an upward trend in overall RMBF with decreasing UPPA was seen, which became significant for a 30% to 45% decline in UPPA (1.07 ± 0.47 versus 0.76 ± 0.37 mL $\cdot$ g $^{-1}$ $\cdot$ min $^{-1}$ [control value]; $p = 0.028$). After this increase a significant reduction in RMBF occurred with the further decline in normalized graft UPPA to less than 55% (0.68 ± 0.44

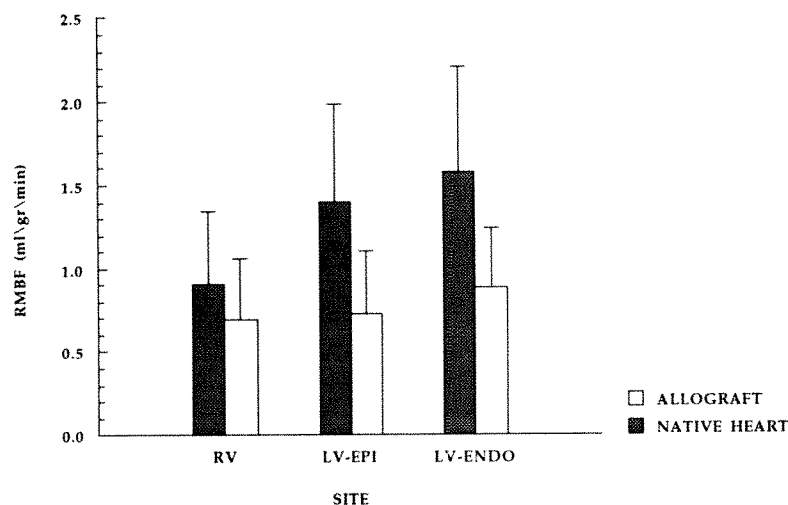
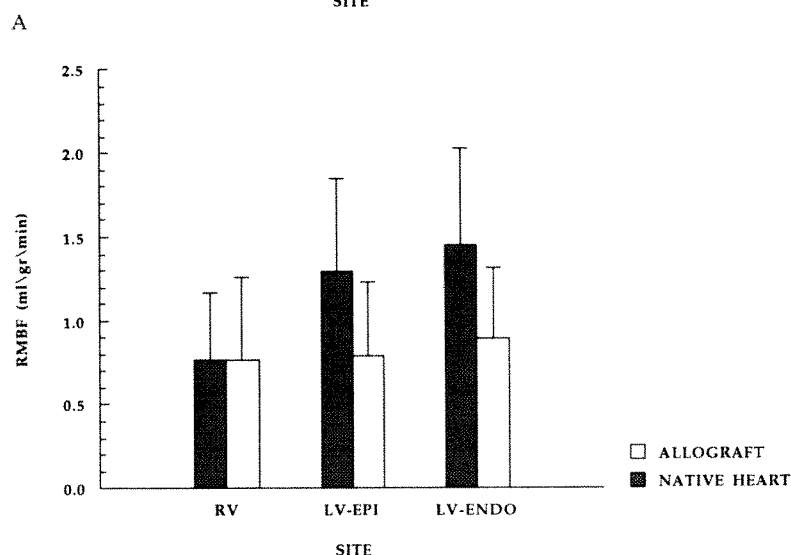


Fig 3. Mean control (A) and overall (B) regional myocardial blood flow (RMBF) for the native hearts and allografts by ventricular site. See text for specific statistical comparisons. (ENDO = endocardium; EPI = epicardium; LV = left ventricular; RV = right ventricle.)



versus $1.07 \pm 0.47 \text{ mL} \cdot \text{g}^{-1} \cdot \text{min}^{-1}$; $p = 0.007$). No difference was seen between overall graft RMBF for normalized graft UPPA less than 55% and graft RMBF during control periods (0.68 ± 0.44 versus $0.77 \pm 0.37 \text{ mL} \cdot \text{g}^{-1} \cdot \text{min}^{-1}$; $p = 0.074$). The biphasic relationship between graft RMBF and normalized graft UPPA was seen for all sites (RV, LV EPI, and LV ENDO) within the grafted hearts.

Allograft Hemodynamics

Figure 5 summarizes the hemodynamic data obtained for the 6 animals studied immediately before sacrifice. It should be noted that all of these measurements were obtained after a decline in UPPA to less than 55% control (during moderate to severe rejection; $RS = 2.41 \pm 0.82$). Mean RV systolic/diastolic pressures for the group were $18.0 \pm 5.3/4.0 \pm 2.5 \text{ mm Hg}$. Mean LV systolic/diastolic pressures for the group were $118.2 \pm 47.5/12.0 \pm 8.9 \text{ mm Hg}$. It is of note that in 4 of 6 dogs the maximal LV systolic pressure was less than or equal to the recipient femoral artery diastolic pressure (maximal pressure gradients be-

tween the graft LV and the recipient femoral artery for the remaining 2 animals were 27 and 70 mm Hg). Blood flow into the graft LV cavity varied widely (20 to 200 mL/min). The mean LV cavity flow was $74.8 \pm 52.3 \text{ mL/min}$.

Comment

This study was designed to examine the relationship between UPPA and cardiac allograft RMBF. Although previous hemodynamic studies have demonstrated a decline in LV RMBF during acute rejection occurring in a setting of non-cyclosporine-based immunosuppression [10-12], those studies did not examine the relationship between the early phases of allograft rejection and RMBF under the influence of CSA. Furthermore, those studies used an orthotopic model of cardiac transplantation that, although comparable with the clinical transplant situation, is complicated by wide variability of myocardial energy demands that could obscure underlying rejection-mediated changes in RMBF. In addition, the time course of this decline in RMBF was unclear; RMBF was shown to

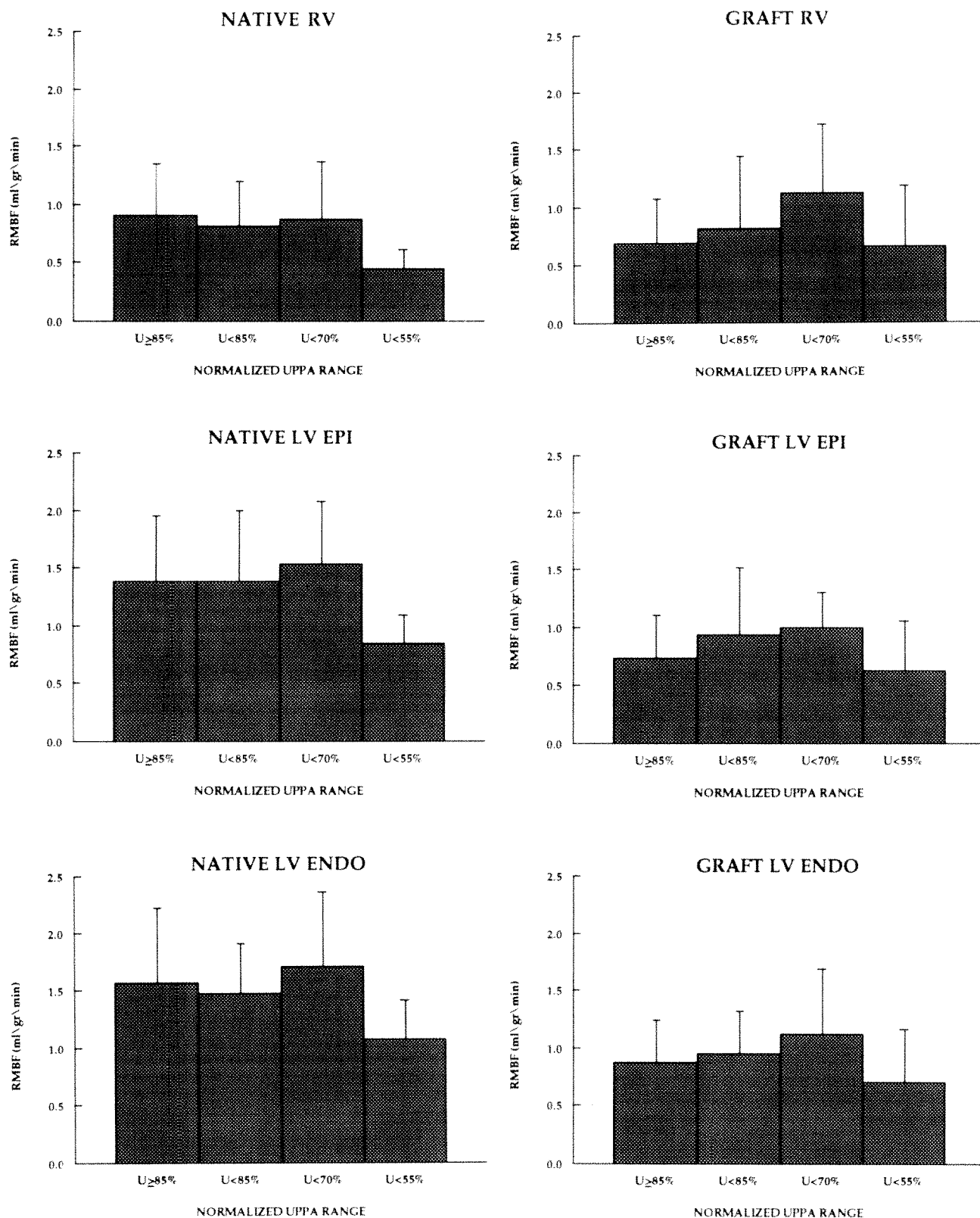


Fig 4. Mean regional myocardial blood flow (RMBF) for the native hearts and allografts by organ, ventricular site, and normalized unipolar peak-to-peak amplitude (UPPA) range. See text for specific statistical comparisons. (ENDO = endocardium; EPI = epicardium; LV = left ventricular; RV = right ventricle.)

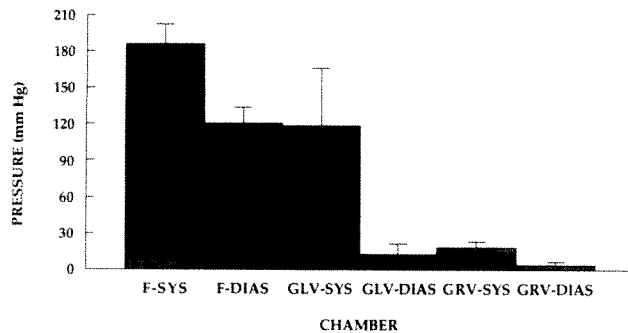


Fig 5. Summary of mean pressure data obtained at the time of terminal hemodynamic study (normalized allograft unipolar peak-to-peak amplitude < 55%). (BP, GLV, and GRV = recipient femoral artery, allograft left ventricular, and allograft right ventricular pressures, respectively; DIAS and SYS = diastolic and systolic pressures, respectively.)

decline as early as 2 to 3 days after transplantation in some studies [10]; however, other studies found no changes in LV RMBF during early rejection, with a decline in RMBF only after the development of marked rejection 8 to 10 days after transplantation [11, 12]. Finally, extrapolation of previous assessments of allograft RMBF to the current clinical setting of cardiac transplantation is difficult, as these previous studies did not use CSA-based immunosuppression, which has been demonstrated to alter the histologic character of rejection [13]. In this study we have measured native and allograft RMBF at times dictated by the telemetrically acquired UPPA data; it has been previously shown that this technique can be used in a prospective manner to accurately monitor cardiac allografts for the onset of rejection in this model [6]. This methodology permitted comparison of histology and RMBF as determined by an independent predictor of the rejection process. This in turn allowed comparison of these two variables at an early stage of rejection that was consistent from animal to animal, a process that would not be possible if EMB and RMBF determinations had been performed on a fixed time schedule.

Endomyocardial Biopsy and Regional Myocardial Blood Flow

Under standard CSA-based immunosuppression the initial stages of histologic rejection, consisting of the development of a perivascular infiltrate without myocyte necrosis, occurred independently of a fall in RMBF. At a time when the rejection process led to a significant decline in UPPA in this study, RMBF was actually increased over the control allograft RMBF value. It should be noted that the average RS at the time of the initial first true-positive UPPA was 1.63 ± 0.45 on a scale of 0 to 4. This corresponds to an earlier stage of histologic rejection than would warrant treatment by conventional clinical practice at this time [6].

Unipolar Peak-to-Peak Amplitude and Regional Myocardial Blood Flow

The results of this study also indicate that a reduction in allograft RMBF does not accompany the decline in UPPA

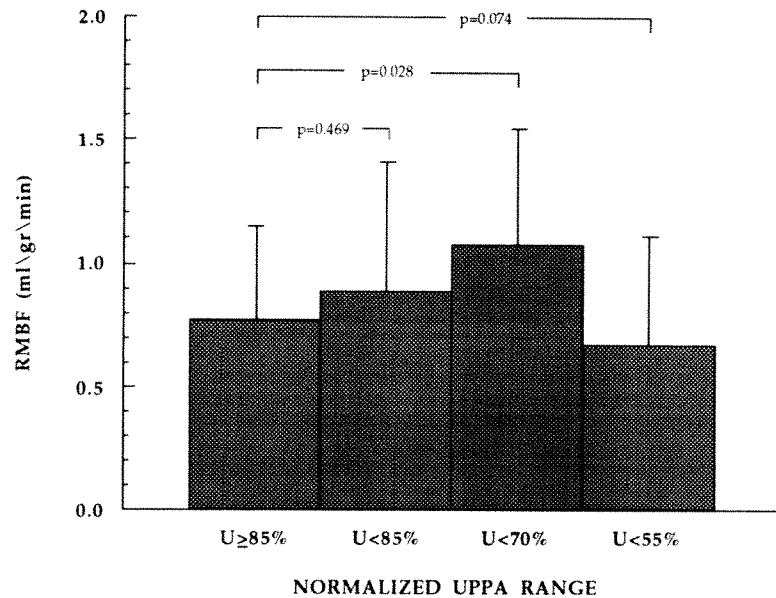
occurring with mild to moderate rejection. Rather, the changes in RMBF that occur during sequential degrees of UPPA decline appear to be biphasic. We observed a small (17%) but not statistically significant increase in allograft RMBF with the initial 15% to 30% decline in UPPA that accompanied histologically mild rejection. A further decline in UPPA (to 30% to 45% of control values) corresponded to the progression of rejection (mild to moderate) and was associated with a significant increase (41%) in overall RMBF. Subsequently, the decline in UPPA associated with severe rejection (UPPA < 55% of control) occurred in conjunction with a reduction in overall RMBF. Although this decline was statistically significant with respect to the RMBF measured during lesser declines in UPPA, it amounted to only an approximately 11% reduction in RMBF from control flows (p = not significant versus control RMBF). This biphasic pattern may reflect the initial acute inflammation occurring during mild to moderate rejecting with subsequent vascular and parenchymal damage developing during severe rejection. These results are similar to those reported by Dumont and associates [12], who, in an orthotopic model, observed no change in allograft RMBF during early rejection but noted a significant decrease during severe rejection. It is of note that in that study there was no method of marking the development of intermediate changes in rejection (ie, the progression of mild to moderate) and thus there was no means of determining interval changes in RMBF.

Control RV, LV ENDO, and LV EPI RMBF measured in this group of native hearts were within the physiologic range of flows previously reported [10, 11]. No change in overall native RMBF was seen with 15% to 45% reductions in allograft UPPA. With greater than 55% declines in UPPA (severe allograft rejection) a 39% reduction in overall native RMBF was seen. Although the fall in RMBF was significant, the absolute native blood flow did not decline to physiologically ischemic levels for LV ENDO ($1.07 \text{ mL} \cdot \text{g}^{-1} \cdot \text{min}^{-1}$) or LV EPI ($0.84 \text{ mL} \cdot \text{g}^{-1} \cdot \text{min}^{-1}$) regions. A more marked decline was seen in the native RV regions ($0.44 \text{ mL} \cdot \text{g}^{-1} \cdot \text{min}^{-1}$; 51% reduction from control). That these reductions in flow did not result in significant native myocardial ischemia is supported by the absence of ischemic changes in UPPAs recorded from native hearts during severe allograft rejection. It is possible that the systemic effects of circulating immune or inflammatory mediators may influence the perfusion of other host organs such as the native heart, thus accounting for the fall in native RMBF.

Heterotopic Hemodynamics

In the heterotopic model employed in this study a low-pressure circuit is present on the right side with graft RV and LV preload determined by coronary flow and flow across the atrial septal defect, respectively. As noted in this study graft RV diastolic pressure ($\approx$ RV preload), even during periods of moderate to severe rejection, is relatively low. The combination of low graft RV preload and the fixed resistance of the atrial septal defect should result in a reduced and relatively constant graft LV preload. Low allograft LV preload in conjunction with dyssynchronous

Fig 6. Mean overall allograft regional myocardial blood flow (RMBF) during the course of study. To the extent that total RMBF represents coronary flow at any given time, the right ventricular preload during early rejection is unchanged. (UPPA = unipolar peak-to-peak amplitude.)



and relatively high afterload (recipient arterial pressure) may result in nonejecting (isovolumic) graft LV function. Analysis of the hemodynamic data obtained in this study supports this. The observed graft LV cavity/recipient femoral artery gradients suggest that, in the heterotopic position, the allograft LV may function largely as an isovolumic preparation. To a lesser extent the heterotopic allograft RV volume may also remain stable; in this preparation RV volume is determined by coronary flow, which remained relatively stable during the course of the study (Fig 6).

It has been shown that significant increases in cardiac tissue volume occur with the edema and cellular infiltration that accompany severe rejection [13], and acute increases in allograft ventricular volume (created with rapid volume infusion or as seen with RV outflow tract obstruction) have been shown to cause a fall in UPPA [6]. Thus myocardial wall or cavity volume changes could contribute to the observed decline in UPPA. Although volume changes may contribute to the marked declines in UPPA that occur in the presence of severe rejection, it is unlikely that volume changes can be invoked as the cause of the initial fall in UPPA because (1) the histology seen in early rejection is marked by minimal cellular infiltration or edema and (2) as discussed above, the heterotopic allograft cavity volumes may be relatively constant over time.

Limitations

The significance of RMBF changes with respect to the presence or absence of ischemia can be completely determined only in the context of myocardial energy demand. Although the hemodynamic data presented here suggest that a major consequence of heterotopic position may be a more constant energy demand than that present in orthotopically placed grafts, precise information regarding allograft heart rate during the various stages of rejection is not available, and hemodynamic assessments were not made during episodes of early rejection. Although it

seems reasonable that the changes in RMBF relate primarily to the sequelae of rejection rather than acute changes in work-related myocardial energy demands, we cannot exclude the possibility that significant increases in myocardial energy demand may be mediated directly by immune cells or circulating inflammatory mediators.

Conclusion

The early immune response during cardiac allograft rejection is focused on the myocardial microvasculature. The results of this study demonstrate that these histologic changes do not occur in association with reduction in absolute global or regional myocardial blood flow. Furthermore, the decline in UPPA that indicates the onset of early histologic rejection occurs despite the maintenance of global and regional blood flow. This suggests that the decline in UPPA is due to electrophysiologic factors that are not mediated by myocardial blood flow per se in this setting.

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Plasma Endothelin Levels and Surgically Correctable Pulmonary Hypertension

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To know the changes in plasma endothelin of patients with pulmonary hypertension, we studied 32 patients with valvular heart disease. Among them, 22 patients had pulmonary hypertension (group I) and 10 had pulmonary arterial pressures in the normal range (group II). Plasma endothelin-1 concentrations of the patients in group I were significantly greater than those of the patients in group II ($p < 0.05$). No significant difference in plasma endothelin-3 concentrations existed between the two groups. Cardiac output and pulmonary capillary wedge pressure had a linear correlation with plasma endothelin-1 levels. There was also a significant correlation between plasma endothelin-1 levels and hemodynamic indicators of severity of pulmonary hypertension, such as mean pulmonary arterial pressure and pulmonary vascular resistance ($p < 0.05$). All patients in this

study underwent surgical procedures for the correction of valvular lesions. All patients in group I showed a decrease in pulmonary arterial pressures, and their plasma endothelin-1 levels decreased from 3.84 ± 0.20 pg/mL to 1.66 ± 0.07 pg/mL ($p < 0.05$), whereas the plasma endothelin-3 levels had only slight variation from 0.64 ± 0.11 pg/mL to 0.75 ± 0.06 pg/mL ($p > 0.05$) between the preoperative and the postoperative stages. The results demonstrated that plasma endothelin-1 rather than endothelin-3 had a role in pulmonary hypertension. Several pieces of evidence pointed out that endothelin-1 functioned as a reactive mediator during vasoconstriction in the case of pulmonary hypertension rather than as a triggering factor of pulmonary hypertension.

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Pulmonary hypertension refers to the abnormal hemodynamic consequence of various conditions that lead to a chronic increase in the pulmonary arterial pressure. The pulmonary arterial pressure is related to the physiologic pulmonary arterial blood flow, the pulmonary venous pressure, and the pulmonary vascular resistance. Chemical and hormonal regulation of pulmonary vascular resistance is a complex and as yet incompletely understood subject. Catecholamine, acetylcholine, prostaglandin, histamine, bradykinin, serotonin, and angiotensin have been reported to play a role in the regulation of pulmonary vascular resistance [1, 2]. However, the exact site where these agents' regulating function occurs within the pulmonary vascular tree is still uncertain.

Furchgott and Zawadzki [3], in 1980, first reported that endothelial cells played a necessary role in determining response to a variety of vasoactive substances. Afterward, some authors have demonstrated the protease-sensitive contractile activity in the supernatants of cultured endothelial cells [4]. All of the above-mentioned experiments indicated that the vasoactive mediators released from endothelial cells played an important role in the regulation of vascular resistance. Hickey and associates [5], in 1985, revealed the existence of an endothelial cell-derived polypeptide with the characteristics of a vasoconstrictor. Yanagisawa and colleagues [6], in 1988, described a 21-amino acid polypeptide (endothelin) that had been suc-

cessfully isolated from cultured porcine endothelial cells. Further experiments [7] have also proved that intravenous administration of endothelin can exert a number of cardiovascular effects, including a sustained, dose-dependent increase in the mean arterial pressure and total peripheral resistance, and a decrease in cardiac output and heart rate. More recently, some authors have reported that endothelin-1 induces contractions in isolated pulmonary vessels and increases pulmonary vascular resistance [8], whereas other experiments have shown that endothelin-1 possesses a vasodilative function in systemic as well as pulmonary circulation [9].

The divergent views regarding the physiological function of endothelin in vascular resistance have been widely discussed. Kohn and associates [10] demonstrated increased plasma endothelin concentrations in patients with essential hypertension. They thought that an increase in the transmural pressure of vessels with the development of hypertension was responsible for the elevation of plasma endothelin levels. Because (1) the reaction to hypertension of endothelial cells in both pulmonary and systemic circulation is similar, (2) endothelin was rapidly processed out of big endothelin in the lungs, and the intensity of activities of processing enzymes was higher than in other tissue as revealed by Kitamura and colleagues [11], and (3) circulating endothelin is rapidly cleared primarily by the lungs as reported by de Nucci and co-workers [12], it has been suggested that the plasma endothelin level will increase when clearance rate decreases or secretion rate of pulmonary endothelial cells increases in some pathological conditions.

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We do not know the relationship between plasma endothelin and pulmonary hypertension. Using surgical correction of valvular heart disease to lower the pulmonary arterial pressure and then comparing the changes of plasma endothelin level before and after operation, we attempted to elucidate the mechanism and physiological role of circulating endothelin in patients with pulmonary hypertension.

Material and Methods

From August 1990 to April 1991, 32 patients with valvular heart disease were studied at National Taiwan University Hospital. Patients' ages ranged from 15 to 70 years with a mean of 48 years. Sixteen patients were male and 16 female. According to the New York Heart Association classification, 10 patients (31%) were in class II, 17 (53%) in class III, and 5 (16%) in class IV. The cause of valvular lesion was recognized in all patients. Rheumatic valvular disease was the cause in 30 patients (94%). Two patients (6%) had degenerative valvular disease. Previous operations on the mitral valve, aortic valve, or both had been performed in 17 patients (53%) 4 to 12 years earlier (mean, 9.4 years). Among them, 15 patients had xenograft tissue valve failure due to calcification or tear of the valve cusp and 2 patients had recurrence of mitral stenosis or insufficiency after a previous reconstructive operation on the mitral valve.

The preoperative hemodynamic study was always carried out within 1 month of the operation. Catheterization of both sides of the heart was routinely performed in each patient to obtain the pressure data in the cardiac chambers and great vessels. Pulmonary arterial pressures consistently in excess of 35 mm Hg systolic, 15 mm Hg diastolic, and 25 mm Hg mean were regarded as indicative of pulmonary hypertension.

Surgical correction of the valvular lesion by way of cardiopulmonary bypass was performed in the usual manner. The postoperative hemodynamic status was evaluated on the fourth postoperative day with a Swan-Ganz catheter, which was inserted immediately after the initiation of anesthesia in the operating room before operation.

For comparison of plasma endothelin-1 and endothelin-3 levels between normal control subjects and the patients with pulmonary hypertension, 10 normal volunteers (average age, 24 years; range, 23 to 25 years) were invited to participate in this study; informed consent was obtained from all patients and volunteers. Central venous blood was collected with the volunteers resting in a supine position for 10 minutes before blood sampling. To observe the changes in plasma endothelin-1 and endothelin-3 levels of patients in this study, blood samples were taken in the same way at the time before operation (patient premedicated, after placement of central venous catheter, but before induction of anesthesia) and 3 months after operation.

The blood samples (10 mL) were put into a chilled syringe right after collection and then transferred into a polypropylene tube containing ethylenediaminetetraace-

tate (1 mg/mL) and aprotinin (500 KIU/mL; Trasylol, Leverkusen, Germany) at 4°C; the tubes were then centrifuged at 3,000 g for 20 minutes at 0°C. The plasma was collected and stored at -70°C until radioimmunoassay. There was no significant correlation between the duration of storage time and levels of endothelin immunoreactivity.

Extraction of Endothelin

Extraction of plasma endothelin was done by a modification of the method previously described [10]. Sep-Columns (Peninsula Laboratories, Inc, Belmont, CA) containing 200 mg of C₁₈ cartridge were activated by washing them with buffer A (60% acetonitrile in 0.1% trifluoroacetic acid; 4 × 1 mL) and then with buffer B (0.1% trifluoroacetic acid; 4 × 5 mL). Each plasma sample was acidified by adding an equal volume of buffer B and then centrifuged at 3,000 g for 15 minutes at 4°C. The mixture of plasma and buffer B was pumped at a rate of 1 mL/min into the activated Sep-Columns. After the Sep-Columns were washed with buffer B (4 × 5 mL), the absorbed endothelinlike materials were slowly eluted with buffer A (3 × 1 mL) into a polypropylene tube. The eluent was completely evaporated with a centrifugal evaporator (Savant Instruments, Inc, Farmingdale, NY). The recovery rate was calculated by adding three different quantities of cold endothelin-1 and endothelin-3 (2 pg/mL, 4 pg/mL, and 8 pg/mL) to plasma with dextran-coated charcoal. The recovery rate was 71% ± 2% for endothelin-1 and 67% ± 4% for endothelin-3.

Radioimmunoassay of Endothelin-1

The plasma endothelin-1 level was measured by using a radioimmunoassay kit for the detection of duplicate samples (endothelin-1; Peninsula Laboratories). The endothelin concentrations were determined by applying antibody to synthetic endothelin-1 and iodine 125-labeled endothelin-1. This antibody cross-reacted 100% with endothelin-1, 7% with endothelin-2, 7% with endothelin-3, and 17% with big endothelin (human). The antibody did not cross-react with α -human atrial natriuretic peptide, angiotensin I, II, and III, vasopressin, adrenocorticotrophic hormone, vasoactive intestinal polypeptide, and big endothelin 22-38 (human). Samples and standards (endothelin-1; Peninsula Laboratories) were dissolved in assay buffer and incubated for 24 hours with rabbit anti-endothelin-1 serum (Peninsula Laboratories) at 4°C. Approximately 12,000 cpm of iodine 125-labeled endothelin-1 was added to each tube and incubated for another 24 hours at 4°C. Diluted normal rabbit serum and goat anti-rabbit immunoglobulin G serum were added on the third day. The contents of each tube were vortex-mixed and incubated at room temperature for 120 minutes. After centrifugation at 1,700 g for 30 minutes, the supernatant was removed by aspiration, and the pellet was counted for iodine 125 with a gamma counter (Packard Cobra Auto-gamma, Canberra Company, Japan). The standard curve was defined by the

Table 1. Salient Preoperative Data of 32 Patients in This Series

Patient No.	Sex	Age (y)	Diagnosis	Preoperative								
				BP (mm Hg)	FC (NYHA)	PAP (mm Hg)	MPAP (mm Hg)	PCWP (mm Hg)	CO (L/min)	PVR (U)	ET-1 (pg/mL)	ET-3 (pg/mL)
1	M	58	MR	146/58	III	60/20	35	18	3.6	4.72	2.87	0.995
2	M	42	(XGT) MS, MR	110/70	III	60/30	45	30	3.9	3.85	3.48	0.225
3	F	62	AR	170/50	III	28/12	18	14	3.1	1.29	2.02	0.589
4	M	59	MR	142/69	II	32/14	22	20	4.7	0.43	3.03	0.754
5	M	48	(XGT) MS	127/86	II	26/14	18	14	4.0	1.00	1.68	0.302
6	F	60	MS, AS, AR	128/74	II	20/10	13	12	5.4	0.19	1.22	1.728
7	F	40	AR	152/72	II	28/8	15	12	4.6	0.65	1.28	0.772
8	M	39	MS, MR	128/85	III	27/12	18	16	5.1	0.39	2.25	1.179
9	M	41	MS, MR, TR	148/87	IV	96/48	64	30	3.2	10.62	6.35	0.401
10	M	46	(XGT) MS	100/60	III	80/18	44	32	4.1	2.93	3.33	0.545
11	F	51	(XGT) AR	146/70	III	24/11	15	10	3.9	1.28	0.78	0.238
12	F	60	AS, AR	125/90	III	93/42	59	38	3.6	5.83	4.50	0.140
13	M	60	(XGT) AS, MR	158/58	IV	95/35	55	22	2.9	11.43	3.67	0.295
14	M	15	MS, MR	80/64	III	50/24	33	28	3.4	1.47	4.07	0.617
15	M	58	(XGT) AR	174/53	IV	55/25	35	28	3.1	2.26	4.62	1.303
16	F	58	(XGT) MS, MR	108/68	II	43/24	30	20	3.8	2.63	2.72	0.216
17	M	29	MS, MR	156/76	III	40/16	25	14	5.2	2.12	2.72	0.327
18	F	47	(XGT) MR	125/71	III	32/16	21	18	4.9	0.61	2.62	0.315
19	F	58	MS, AR	191/89	III	65/25	40	30	3.8	2.63	2.92	0.322
20	M	38	(XGT) MS	139/72	III	50/36	44	26	5.0	3.60	3.58	0.534
21	F	51	OMC s/p, MS	111/54	III	38/19	27	15	3.8	3.16	3.82	0.478
22	F	69	AS	145/64	II	50/20	30	20	3.1	3.23	3.79	0.475
23	F	25	AR	140/50	II	25/9	16	11	6.0	0.83	1.41	0.417
24	F	42	MS	143/67	III	80/30	50	24	3.9	6.67	3.62	2.195
25	M	60	AS	91/71	IV	70/35	47	32	3.4	4.41	5.21	0.416
26	F	40	(XGT) MS	105/53	II	40/26	31	25	4.9	1.22	3.12	0.064
27	M	70	(XGT) MR, AR	170/80	III	56/38	44	30	4.5	3.11	3.38	1.496
28	M	32	MVP s/p, MR	102/54	III	62/24	37	28	3.9	2.31	4.13	1.052
29	F	70	(XGT) MS, MR	140/50	II	42/16	26	16	4.8	2.08	2.78	0.844
30	F	35	(XGT) MS, MR	131/46	II	34/14	21	15	5.3	1.13	2.12	0.773
31	F	38	(XGT) MS, MR	108/72	IV	74/32	46	28	4.2	4.29	4.67	0.685
32	M	42	(XGT) MS, MR	132/76	III	83/41	55	32	3.5	6.57	5.08	0.544

AR = aortic regurgitation; AS = aortic stenosis; BP = systemic blood pressure; CO = cardiac output; ET = endothelin; FC = functional class; MPAP = mean PAP; MR = mitral regurgitation; MS = mitral stenosis; MVP s/p = previous mitral valvuloplasty; OMC s/p = previous open mitral commissurotomy; NYHA = New York Heart Association; PAP = pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; XGT = xenograft tissue valve failure.

equation: $\logit B/B_0 = 9.85193 - 0.101576 \log \text{pg endothelin-1}$ ($r^2 = 0.99$). The lower limit of detection was 1.0 pg/tube. The interassay variation was 8.4% and the intraassay variation was 6.8%.

Radioimmunoassay of Endothelin-3

The plasma endothelin-3 level was measured by using a radioimmunoassay kit (endothelin-3; Peninsula Laboratories) the same way as for plasma endothelin-1. The kit had an antibody that cross-reacted less than 2% with endothelin-1, 1% with endothelin-2, 0.001% with sarafotoxin S₆B, and 0.01% with brain natriuretic peptide 26 (porcine), and did not cross-react with angiotensin II, arginine-vasopressin, α -atrial natriuretic peptide (human), vasoactive intestinal polypeptide, and substance P. The standard curve was as follows: $\logit B/B_0 = 10.0485 - 0.103885 \log \text{pg endothelin-3}$ ($r^2 = 0.99$). The interassay and intraassay

variation were 8.6% and 6.3%, respectively. The lower limit of detection was 1.0 pg/tube.

Statistical Analysis

Group data are presented as mean $\pm$ standard error. For the comparison of endothelin values of the patients with and without pulmonary hypertension, one-way analysis of variance was performed. Paired *t* test was used to assess the change in plasma endothelin concentration from preoperative to postoperative stage. For the comparison of the associated significance between each event and plasma endothelin levels, linear regression analysis was used to check the effect of each variable on the elevation of endothelin level in plasma. Kruskal-Wallis analysis was used to study the relation of the plasma endothelin concentrations to the New York Heart Association func-

Table 2. Salient Postoperative Data of 32 Patients in This Series

Patient No.	Surgical Procedure	Postoperative								
		BP (mm Hg)	FC (NYHA)	PAP (mm Hg)	MPAP (mm Hg)	PCWP (mm Hg)	CO (L/min)	PVR (U)	ET-1 (pg/mL)	ET-3 (pg/mL)
1	MVP	109/43	I	26/11	16	11	4.9	1.02	1.81	0.684
2	Redo MVR	120/60	I	18/7	11	8	4.4	0.68	1.26	1.002
3	AVR	128/59	I	20/13	15	11	3.8	1.05	2.08	1.836
4	MVR	118/82	I	26/8	14	8	5.3	1.13	1.14	0.351
5	MVR	123/80	I	26/13	17	14	5.2	0.58	1.70	0.514
6	DVR	116/78	I	24/14	17	12	5.5	0.91	1.18	0.579
7	AVR	122/75	I	26/10	15	12	6.4	0.47	1.20	0.792
8	MVR	120/81	I	20/10	13	11	5.6	0.36	1.85	0.479
9	MVR, TVP	140/73	II	28/18	21	14	3.7	1.89	2.31	1.155
10	Redo MVR	136/47	I	24/10	15	12	4.1	0.73	2.01	0.793
11	Redo MVR	138/82	I	23/8	13	9	4.3	0.93	0.93	1.507
12	AVR	145/72	I	28/10	16	12	5.3	0.75	1.43	0.091
13	Redo DVR	126/80	I	24/11	15	9	5.4	1.11	1.60	0.398
14	MVP	127/62	I	33/14	20	14	4.8	1.25	1.49	0.586
15	Redo AVR	109/60	I	19/8	12	7	4.0	1.25	1.28	0.253
16	Redo MVR	112/80	I	24/13	17	12	3.9	1.28	1.60	0.344
17	MVR	113/53	I	20/8	12	9	5.5	0.55	1.12	0.607
18	Redo MVR	127/60	I	20/6	11	9	5.2	0.38	1.80	1.352
19	DVR	112/60	I	22/8	16	8	4.8	1.67	1.64	0.891
20	Redo MVR	139/80	I	24/11	15	6	5.0	1.80	2.38	0.644
21	MVR	100/60	I	18/6	10	3	4.9	1.43	1.45	0.769
22	AVR	103/63	I	24/12	16	12	3.9	1.03	1.62	0.697
23	AVR	124/74	I	18/10	15	8	5.8	1.21	1.47	0.325
24	OMC	100/53	I	16/8	11	8	3.9	0.77	1.34	0.732
25	AVR	117/63	II	28/20	24	10	4.6	3.04	1.51	1.108
26	Redo MVR	121/61	I	32/20	24	18	4.9	1.22	2.60	1.013
27	Redo MVR	95/44	I	24/12	16	14	5.0	0.40	1.89	0.993
28	Redo MVR	115/69	I	26/8	14	12	4.0	0.50	1.45	0.847
29	Redo MVR	146/82	I	27/11	16	11	4.7	1.06	1.11	0.747
30	Redo MVR	124/70	I	16/4	8	4	5.1	0.78	1.54	0.723
31	Redo MVR	118/80	I	20/10	13	5	4.5	1.78	1.62	0.976
32	Redo MVR	120/80	I	27/12	17	9	3.9	2.05	2.01	1.084

AVR = aortic valve replacement; BP = systemic blood pressure; CO = cardiac output; DVR = double-valve replacement; ET = endothelin; FC = functional class; MPAP = mean PAP; MVP = mitral valvuloplasty; MVR = mitral valve replacement; NYHA = New York Heart Association; OMC = open mitral commissurotomy; PAP = pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; TVP = tricuspid valvuloplasty.

tional classification. The level of significance was taken to be p less than 0.05.

Results

The characteristics of the 32 patients in this study are shown in Tables 1 and 2. Twenty-two patients had pulmonary hypertension (group I), among whom the highest pulmonary arterial pressures were 96 mm Hg systolic, 48 mm Hg diastolic, and 64 mm Hg mean pulmonary arterial pressure. Their average systolic, diastolic, and mean pulmonary arterial pressures were 63 mm Hg, 28 mm Hg, and 41 mm Hg, respectively. The mean pulmonary capillary wedge pressure was 26 mm Hg for the 22 patients in group I, with the highest pressure being 38 mm Hg. Ten patients with valvular heart disease had pulmonary arterial pressure within normal limits (group

II). The average systolic, diastolic, and mean pulmonary arterial pressure and the pulmonary capillary wedge pressure recorded in group II were 28 mm Hg, 12 mm Hg, 18 mm Hg, and 14 mm Hg, respectively.

The preoperative plasma endothelin-1 concentrations ranged from 2.72 pg/mL to 6.35 pg/mL with a mean of 3.84 ± 0.20 pg/mL in group I and from 0.78 pg/mL to 3.03 pg/mL with a mean of 1.84 ± 0.22 pg/mL in group II. Therefore, plasma endothelin-1 levels of the patients with pulmonary hypertension were significantly greater than those of the patients without pulmonary hypertension ($p < 0.05$) (Table 3). The preoperative plasma endothelin-3 concentrations were 0.64 ± 0.11 pg/mL in group I and 0.71 ± 0.15 pg/mL in group II. The plasma endothelin-1 concentrations of the normal volunteers (ranging from 1.33 to 3.01 pg/mL with a mean of 1.76 ± 0.16 pg/mL) showed a statistically significant difference between the

Table 3. Plasma Endothelin Concentrations

Group	Plasma ET-1 level (pg/mL)			Plasma ET-3 level (pg/mL)		
	Preoperative	Postoperative	Change	Preoperative	Postoperative	Change
With PHT (n = 22)	3.84 ± 0.20 ^a	1.66 ± 0.09 ^b	2.18 ± 0.20	0.64 ± 0.11	0.75 ± 0.06	-0.10 ± 0.12
No PHT (n = 10)	1.34 ± 0.22	1.49 ± 0.12	0.35 ± 0.20	0.71 ± 0.15	0.85 ± 0.17	-0.14 ± 0.26
Total (n = 32)	3.21 ± 0.22 ^a	1.61 ± 0.07 ^b	1.61 ± 0.21	0.66 ± 0.09	0.78 ± 0.07	-0.11 ± 0.11
Control (n = 10)	1.76 ± 0.16			0.79 ± 0.13		

^a $p < 0.05$ compared with control group. ^b $p < 0.05$ compared with preoperative data.

ET = endothelin; PHT = pulmonary hypertension.

normal volunteers and the patients with pulmonary hypertension ($p < 0.05$), but there was no significant difference between the normal volunteers and the patients without pulmonary hypertension ($p > 0.05$). There was also no significant difference in plasma endothelin-3 levels between group I, group II, and normal volunteers (0.79 ± 0.13 pg/mL).

Cardiac output had a inverse linear correlation with plasma endothelin-1 levels (Fig 1). Pulmonary capillary wedge pressure was positively correlated with plasma endothelin-1 levels (Fig 2), and positive linear correlations also existed between plasma endothelin-1 level and hemodynamic indicators of severity of pulmonary hyperten-

sion such as pulmonary vascular resistance (Fig 3) and mean pulmonary arterial pressure (Fig 4). Similarly, there were significant correlations between plasma endothelin-1 level and the preoperative functional class (Fig 5; Table 4). No significant correlation existed between plasma endothelin-1 levels and systemic arterial pressures, type of valvular lesions, or surgical procedures. Neither could significant correlation be observed between the plasma endothelin-3 levels and such parameters as indicators of severity of pulmonary hypertension, cardiac output, preoperative functional class, systemic arterial pressure, type of valvular lesions, or surgical procedures. Fifteen patients had a xenograft tissue valve failure,

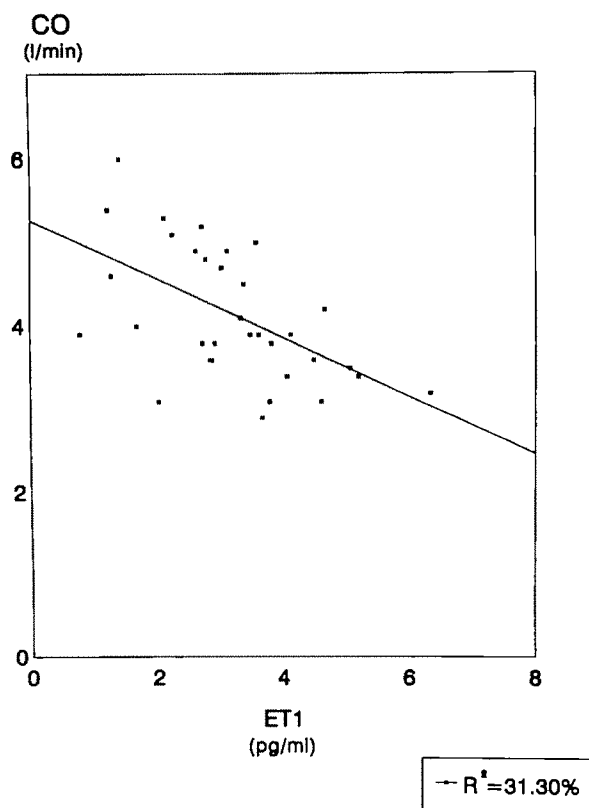


Fig 1. Preoperative cardiac output (CO) had a linear correlation with plasma endothelin-1 (ET1) levels ($p < 0.05$).

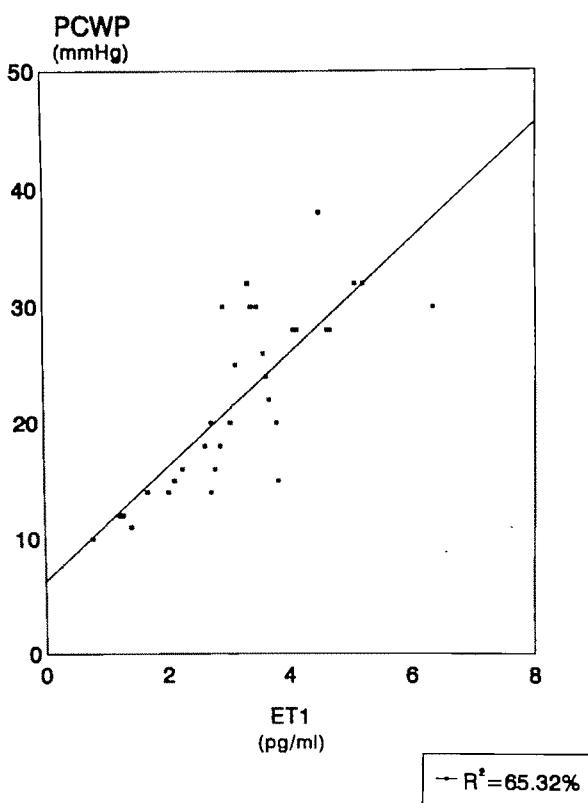


Fig 2. Preoperative pulmonary capillary wedge pressure (PCWP) had a linear correlation with plasma endothelin-1 (ET1) levels ($p < 0.05$).

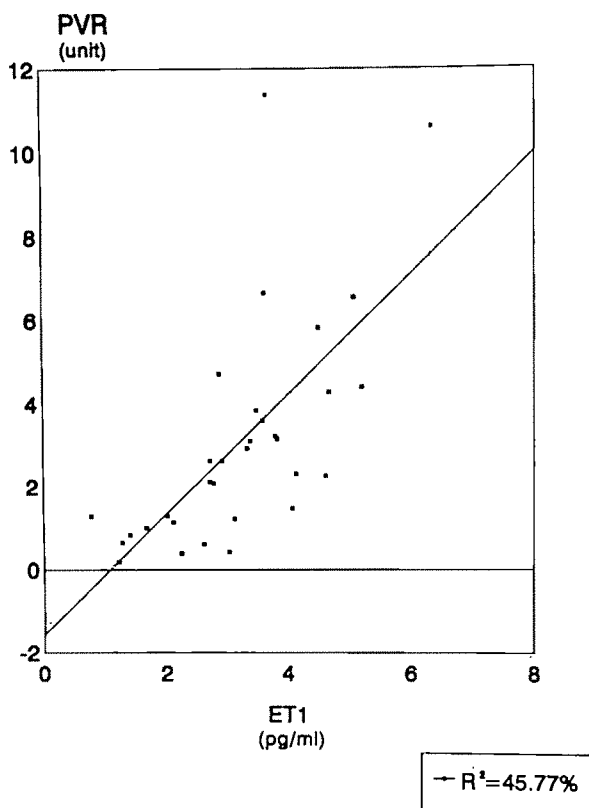


Fig 3. Preoperative pulmonary vascular resistance (PVR) had a linear correlation with plasma endothelin-1 (ET1) levels ($p < 0.05$).

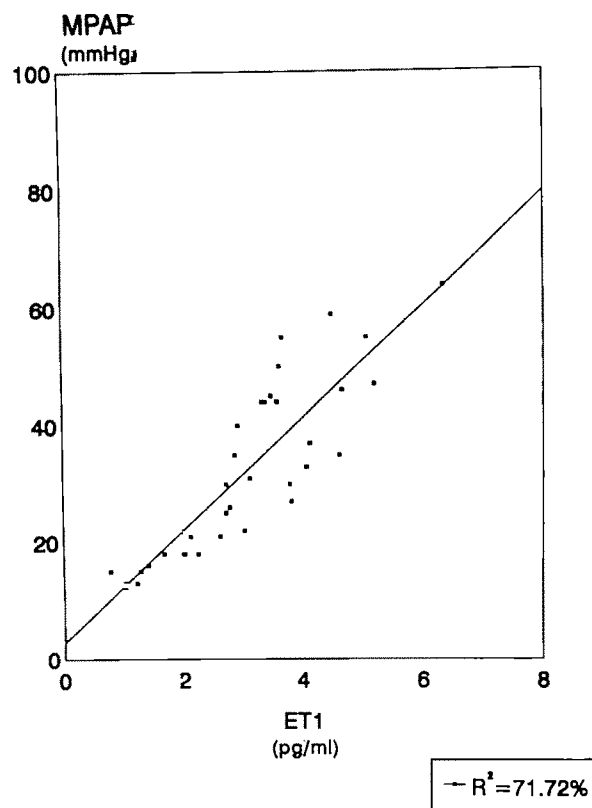


Fig 4. Preoperative mean pulmonary arterial pressure (MPAP) had a linear correlation with plasma endothelin-1 (ET1) levels ($p < 0.05$).

whereas 17 patients had a native valve lesion. No significant difference in plasma endothelin-1 concentrations and plasma endothelin-3 can be demonstrated between the group with xenograft tissue valve failure and the group with native valve lesion (Table 5).

After surgical correction of the valvular lesion, the pulmonary arterial pressure of all patients in group I decreased into the normal range. The plasma endothelin-1 levels ranged from 1.11 pg/mL to 2.60 pg/mL with a mean of 1.66 ± 0.09 pg/mL in group I. Compared with the preoperative value (3.84 ± 0.20 pg/mL), the plasma endothelin-1 level decreased significantly ($p < 0.05$) (Fig 6). There was no statistically significant difference in plasma endothelin-1 and endothelin-3 levels between the normal volunteers and the patients in both group I and group II during the postoperative period (see Table 3). The reduction in pulmonary arterial pressure after surgical correction of the valvular lesion in patients with pulmonary hypertension was always associated with a decrease in plasma endothelin-1 level.

Clinical status of all patients in this study has improved. Thirty patients are in functional class I and 2 in class II. The improvement in functional class was always associated with a decrease in plasma endothelin-1 level in patients with pulmonary hypertension.

Comment

Endothelin is a novel vasoconstrictor peptide composed of three iso peptides (endothelin-1, -2, and -3), each of

which has a unique sequence of amino acids. Endothelin-1 is synthesized by vascular endothelial cells; endothelin-3 is present in a porcine brain homogenate and may be

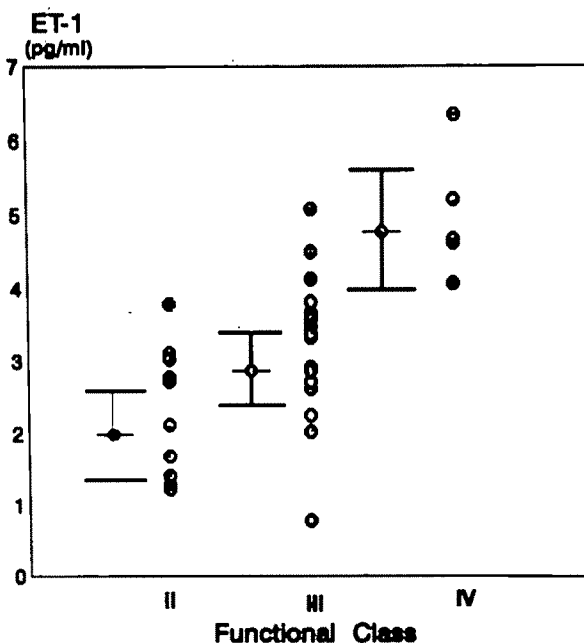


Fig 5. Plasma endothelin-1 (ET-1) level significantly elevated as the functional class increased ($p < 0.05$).

Table 4. Plasma Endothelin Levels According to Functional Class

Endothelin	Preoperative Functional Class			Postoperative Functional Class	
	II (n = 10)	III (n = 17)	IV (n = 5)	I (n = 30)	II (n = 2)
ET-1 (pg/mL)	2.315 ± 0.284 ^a	3.222 ± 0.243 ^b	4.984 ± 0.386	1.587 ± 0.070	1.910 ± 0.400
ET-3 (pg/mL)	0.635 ± 0.148	0.675 ± 0.133	0.684 ± 0.164	0.754 ± 0.068	1.132 ± 0.023

^a $p < 0.05$, class II versus class III, class II versus class IV. ^b $p < 0.05$, class III versus class IV.

ET = endothelin.

a neuronal form of endothelin; endothelin-2, however, has not been identified in any tissue. Because endothelin-3 and endothelin-1 can exert potent vasoconstrictive effects on pulmonary arteries [13], they were thought to play a role in pulmonary physiology. Our results clearly demonstrated that the fluctuation of plasma endothelin-1 levels, but not endothelin-3, was concomitant with the severity of pulmonary hypertension. This pointed out the possibility that (1) vascular endothelial cells were the major source of plasma endothelin secreted in patients with pulmonary hypertension and (2) endothelin-3 had little interrelation with the occurrence of pulmonary hypertension.

Our results clearly demonstrated that preoperative plasma endothelin-1 levels were elevated in patients with pulmonary hypertension after valvular heart disease. Steward and associates [14] had a similar result. They pointed out that plasma endothelin-1 levels were elevated not only in patients with primary pulmonary hypertension, but also in patients with secondary pulmonary hypertension associated with hypoxic lung disease, congenital heart disease, collagen vascular disease, pulmonary thromboembolism, and valvular heart disease. The cause resulting in elevation of plasma endothelin-1 level is not yet known. Some authors suggested that the elevation of plasma endothelin-1 level was related to a decrease in its clearance in the lungs. However, as both endothelin-1 and endothelin-3 were cleared mainly through the pulmonary circulation [15], the constant level of endothelin-3 in plasma, as shown in Table 1, indicated that the clearance rate of endothelin in the lung was not impaired in patients with pulmonary hypertension.

There are two possible explanations for the elevated plasma endothelin level in pulmonary hypertension. One possibility is that elevated levels of plasma endothelin might be caused by an increase in metabolic rate of endothelial cells in the pulmonary circulation. The basal

replication rate in the normal vascular endothelial cells is usually 0.15% [16]. Increased endothelial replication has been described in endotoxemia [17] as well as during hypertension [16]. Previous studies have also revealed that plasma endothelin-1 concentrations were elevated both in patients with hypertension [10] and in rats intravenously administered endotoxin [18]. The increased metabolic rate of vascular endothelial cells may facilitate the synthesis of endothelin. Although endothelial cells in pulmonary circulation do not proliferate in pulmonary hypertension, they probably increase their rates of degradation and production. The increase in metabolic rate of endothelial cells in the pulmonary circulation might accelerate the synthesis of messenger RNA of endothelin and its related protein end-product, and thus increase the plasma levels of endothelin-1.

Another explanation for elevated plasma endothelin-1 level is the flow stasis in the pulmonary circulation after pulmonary venous hypertension. Wagner and colleagues [19] observed that plasma endothelin-1 concentrations increased significantly within 10 minutes after venous stasis in the forearm had occurred. The similar result of our study to Wagner's, although the conditions were different, clearly demonstrated that venous hypertension induced through venous obstruction increased the plasma endothelin-1 levels. The increased secretion rate of endothelin might be a result of the interaction between other vasoactive substances and vascular endothelial cells.

Elevated plasma endothelin-1 levels may play an important physiological role in pulmonary hypertension. Unlike the systemic vascular bed, in which both vasodilation and vasoconstriction control blood flow, the pulmonary vascular wall is controlled mainly by vasoconstriction. Under normal conditions, pulmonary vasculature is nearly maximally dilated to permit gas exchange. Prostacyclin may play a role in maintaining this normal level of low pulmonary vascular tone. A previous study [2] has

Table 5. Plasma Endothelin Concentrations of Patients With and Without Xenograft Tissue Valve Failure

Group	Plasma ET-1 Level (pg/mL)			Plasma ET-3 Level (pg/mL)		
	Preoperative	Postoperative	Change	Preoperative	Postoperative	Change
XGT (n = 15)	3.18 ± 0.30	1.69 ± 0.12 ^a	1.49 ± 0.28	0.56 ± 0.11	0.82 ± 0.09	-0.26 ± 0.15
No XGT (n = 17)	3.25 ± 0.39	1.53 ± 0.08 ^a	1.71 ± 0.32	0.76 ± 0.13	0.74 ± 0.09	0.02 ± 0.16

^a $p < 0.05$ compared with preoperative plasma endothelin levels.

ET-1 = endothelin-1; ET-3 = endothelin-3; XGT = xenograft tissue valve failure.

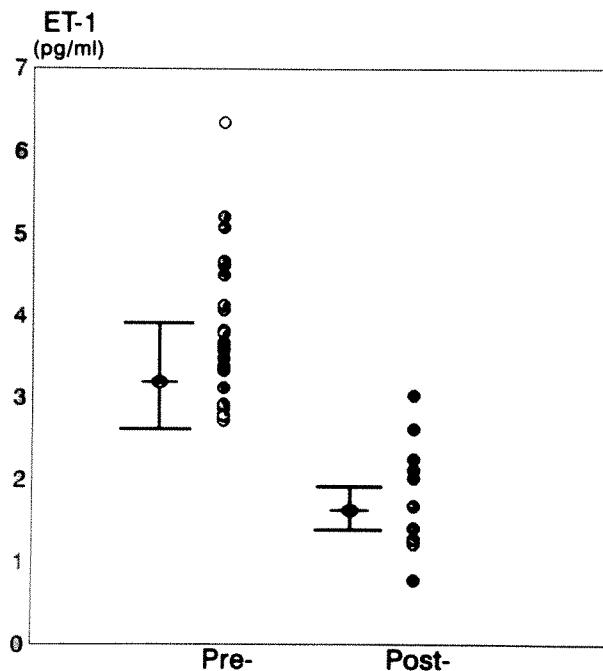


Fig 6. Postoperative (Post-) endothelin-1 (ET-1) levels dropped significantly as compared with the preoperative (Pre-) values.

demonstrated that pulmonary arterial pressure and pulmonary vascular resistance decreased markedly in patients with pulmonary hypertension who received an intravenous infusion of prostacyclin. Recent reports have indicated that endothelin stimulates the release of prostacyclin. Resink and Scott-Burclen [20] revealed that phospholipase A_2 can be activated by endothelin, causing metabolism of arachidonic acid to occur via the lipooxygenase pathway. De Nucci and associates [12] reported that the infusion of endothelin into the perfused lung induced an increase in the level of a stable metabolite of prostacyclin, 6-keto-prostaglandin $F_{1\alpha}$. Furthermore, Fola and associates [21] observed that endothelin had significant dilatory properties that were opposed by its constrictor action at higher doses. They also noted that endothelin-induced dilation in vessels occurred through a cyclooxygenase product-mediated mechanism. In our present experiment, plasma endothelin-1 concentrations were elevated up to 6.35 pg/mL, nearly four times the control levels in patients with pulmonary hypertension; however, the elevated plasma endothelin-1 concentrations were still below the threshold for the induction of vasoconstriction in humans [7]. This peptide, secreted in patients with pulmonary hypertension, may result in prostacyclin secretion, pulmonary vasodilation, and then a decrease in pulmonary vascular resistance.

On the other hand, elevated plasma endothelin-1 levels may be correlated with proliferation of the cells of the vessel wall in pulmonary hypertension. The morphology of the lungs in pulmonary venous hypertension after mitral valve disease is distinctive, and the veins, arteries, and parenchyma are affected. Medial hypertrophy and proliferation of smooth muscle cells are inevitably seen in

veins and arteries in the pulmonary circulation. Komuro and associates [22] reported that endothelin-1 can cause smooth muscle cells to proliferate. The increased secretion of endothelin from endothelial cells may stimulate and further aggravate pathological changes in underlying intima and media of pulmonary vasculature in pulmonary hypertension.

The elevation of pulmonary arterial pressures is observed in many patients with mitral or aortic valve disease. This is a combined result of the back-transmission of elevated left atrial pressures and elevated pulmonary vascular resistance. Our data demonstrated that after surgical correction of the defective valve, severe pulmonary hypertension will regress toward normal, most probably due to the sudden reduction of left atrial pressures and to the reversal of severe spastic pulmonary vasoconstriction that accompanies left atrial hypertension in some patients. Although this initial reduction appears rapidly in most patients, pulmonary vascular resistance sometimes will continue to fall further in the months after operation [23]. Because hemorrhage and surgical procedures resulted in a high level of plasma endothelin [24], the postoperative samples were collected 3 months after operation to avoid interference. Our data showed that plasma endothelin-1 levels and pulmonary arterial pressures synchronously elevated in patients with valvular heart disease according to the severity of pulmonary hypertension, and both of them decreased soon after surgical correction of the diseased valve in the heart. The reversible change in plasma endothelin-1 levels indicated that endothelin-1 was a reactive mediator the release of which was stimulated by the altered resistance of pulmonary venous drainage. Because (1) the maximal plasma endothelin-1 levels in patients with pulmonary hypertension were far below the concentrations required for inducing vasoconstriction; (2) most patients with uremia, diabetes mellitus, and vasculitis had increased plasma endothelin-1 levels [25] without elevated pulmonary arterial pressures; and (3) the elevated plasma endothelin-1 levels in patients with pulmonary hypertension returned to the levels seen in normal control subjects after decrease of pulmonary arterial pressure, we consider endothelin-1 to be a reactive mediator of vasoconstriction in pulmonary hypertension rather than a triggering factor of pulmonary hypertension.

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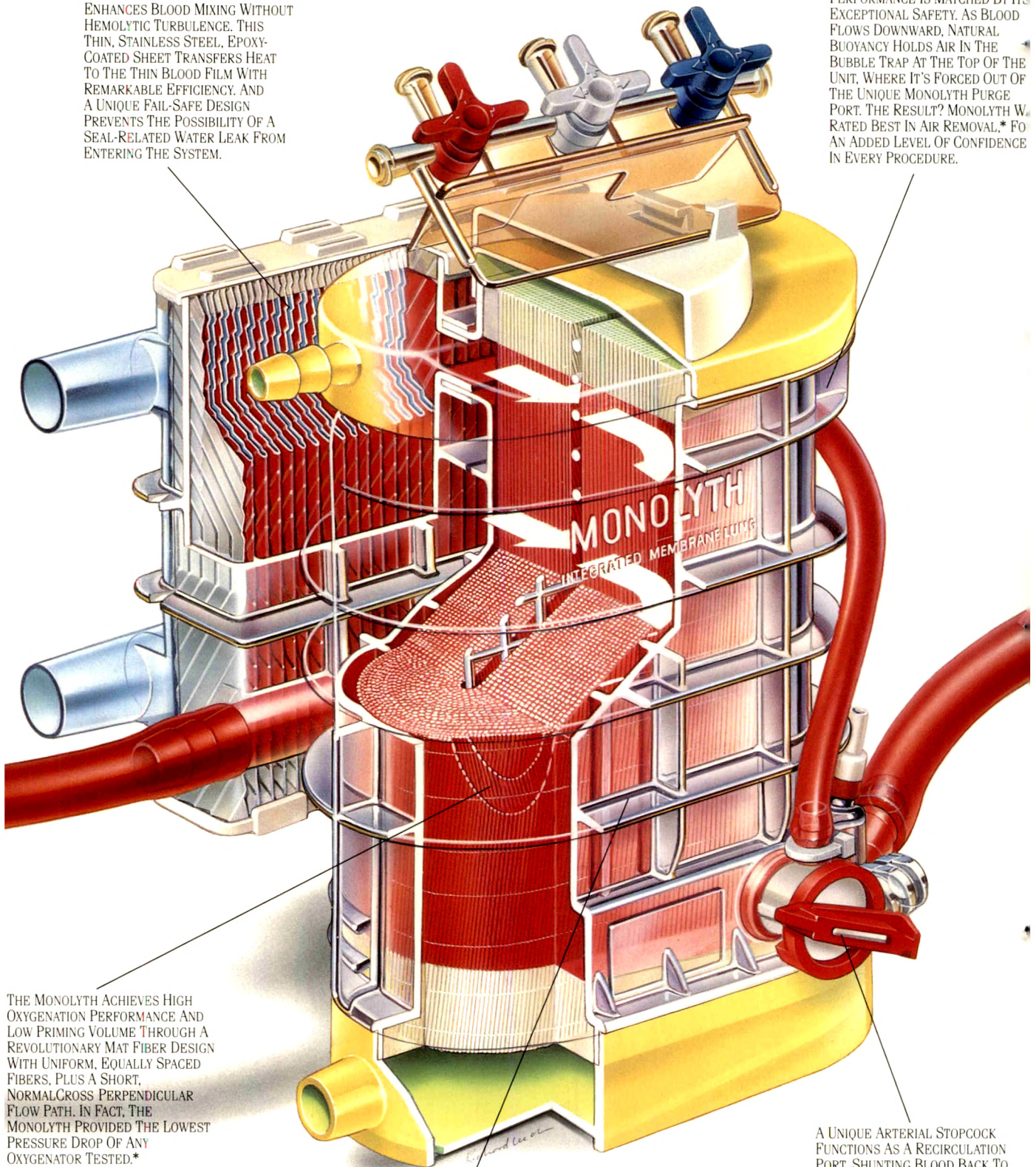
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Primary Closure for Infected Dehiscence of the Sternum

J. Ernesto Molina, MD, PhD

Department of Surgery, University of Minnesota, Minneapolis, Minnesota

I propose a new irrigation-suction system to achieve primary closure of the sternum in cases of postoperative infected dehiscence. Of 16 cases, I had no treatment failures, no recurring infections, and no patient deaths after 1 to 8 years of follow-up. The new system entails retrosternal and superficial sets of tubes,

both in double-staggered position, with primary closure of the sternum and of the skin. Skin or muscle flaps are avoided, and the stability of the chest cage is maintained. Hospitalization time is 14 to 18 days.

(*Ann Thorac Surg* 1993;55:459-63)

Managing purulent sternal infections with dehiscence and mediastinitis has received frequent attention during the past few years [1-8]. Dehiscence of the sternotomy after cardiac procedures without infection is simply taken care of by rewiring and proper prophylactic antibiotics. However, dehiscence with infection is a more complex problem and has led to a wide variety of treatments.

This condition carries significant mortality even at present [8-10]. Despite successful reports in the literature using primary reclosure, all described techniques have a high failure rate [2, 7, 11-14]. Many cardiac surgeons do not even attempt treatment without consulting plastic surgeons, who usually use muscle, omental, or skin flaps to fill the gap of the dehiscence [1, 2, 5, 12, 15, 16]. This means long hospitalization, complex operation, and chest cage instability until the healing is completed. Any future cardiac reoperation is difficult or impossible.

I contend that all these cumbersome procedures can be totally averted by implementing an aggressive approach as soon as the complication is diagnosed. My approach uses a new irrigation-suction system, combined with an effective rewiring technique described in the next section.

Material and Methods

I treated a total of 16 consecutive patients in whom purulent sternotomy dehiscence developed between 1982 and 1991 at the University of Minnesota with this new approach. During the same period, 6,530 patients underwent open cardiac operations using a midline sternotomy incision (rate of purulent sternotomy dehiscence, 0.24%). Patient age ranged from 17 months to 73 years. Diagnosis of the infection was made from 5 to 46 days after the original operation. I excluded from this study patients who sustained sternotomy dehiscence without infection

and thus were promptly rewired without any complications.

The cardiac procedures the patients underwent are listed in Table 1. Infective organisms were identified as *Staphylococcus aureus* or *Staphylococcus epidermidis*, which comprised 62.5% of the cases (10 patients). The next most frequent organism was *Enterococcus* at 12.5% (2 patients), followed by *Enterobacter* at 12.5% (2 patients), and mixed flora at 12.5% (2 patients). All patients were treated with the same irrigation-suction system, except that smaller tubes were used in children.

Surgical Technique

As soon as the diagnosis was made, the patients underwent operation on an urgent basis. Before the operation, they began receiving intravenous antibiotics. The most common antibiotic used was cefamandole at the dosage of 2 g intravenously every 6 hours for 2 weeks. Other antimicrobial agents were used in the remaining patients according to the organism sensitivity.

Under general anesthesia, the sternotomy was totally reopened. Pressurized water jet irrigation-debridement with antibiotic solution (usually cephalothin at 0.1% concentration) was carried out. I used the Sumpulse lavage system manufactured by the Davol Company (Cranston, RI), with a splash shield 16.5 cm in diameter. The system is connected to a compressed air tank to give the jet of water the proper strength to mobilize the necrotic material. The undersurface of the sternum is surgically mobilized to the lateral border, passing it for about 1.25 cm. If the infection has been present for more than a week, this maneuver is usually very tedious and difficult to do. However, with careful hemostasis using the cautery, it has always been accomplished without complications.

Owing to the absence of tissue planes beyond 2 weeks after operation, no blunt dissection should be attempted. This could tear either the cardiac tissue or other soft structures in the anterior mediastinum; consequent bleeding is difficult to control. Therefore, sharp dissection with cautery is recommended until the entire undersurface of the sternum is completely detached from the mediastinal

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Table 1. Distribution of Patients According to Original Operation Performed and Time of Sternal Dehiscence/Reoperation

Patient No.	Age (y)	Sex	Weight (kg)	Initial Type of Operation	Time of Sternal Repair (days)	Diabetes	Obesity
1	61	M	103	CABG × 3	6	...	Yes
2	1½	M	10.2	Redo VSD	11	...	...
3	70	M	65.2	CABG × 4	12	...	...
4	73	F	80.3	CABG × 3	33	...	...
5	61	M	88.3	CABG × 4	10	...	...
6	56	M	65	CABG × 4	22	...	...
7	2½	M	9.1	A-V canal	25	...	...
8	62	M	100.9	CABG × 7	5	...	Yes
9	69	F	72	CABG × 2, MVR	10	...	...
10	59	M	91	CABG × 3, IABP	17	...	...
11	49	M	102	CABG × 3	9	Yes	Yes
12	41	F	77.4	CABG × 2	46	Yes	Yes
13	68	M	73	CABG × 4	5	...	...
14	59	F	79	Redo AVR	29	...	...
15	62	M	81.6	CABG × 4	17	...	...
16	64	M	74	CABG × 2	7	...	...

A-V canal = atrioventricular canal; AVR = aortic valve replacement; CABG = coronary artery bypass grafting; IABP = intraaortic balloon pump; MVR = mitral valve replacement; VSD = ventricular septal defect.

tissues and the heart. After both sides are completed in this manner, the anterior surface of the sternum must be laterally exposed using dissection and irrigation. Only the intercostal spaces are needed to allow a reinforcing wire to be placed and laced around each rib, up to the manubrium and back as described by Robicsek and associates [17]. Their technique was originally aimed at preventing sternal dehiscence (Figs 1, 2).

After the mediastinum has been thoroughly irrigated with antibiotic solution and debrided, a deep system of irrigation and suction tubes is implanted. The tubes are staggered to ensure effective irrigation and suction along the entire length of the sternum. Two sets of tubes must be implanted: one deep behind the sternum and one superficially over the sternum between it and the skin.

The irrigation tubes are usually small, 14F or 16F, and the suction tubes are 24F to 28F. To effectively irrigate the upper part of the understernum, an irrigation tube is needed with an accompanying staggered suction tube at that level. Another similar pair is placed to provide irrigation to the lower part of the retrosternum (Fig 3). To avoid confusion for the nursing personnel and house staff, all tubes from the deep system (retrosternal) are always brought out on the right side in the upper part of the abdomen. Tubes are secured to the skin, making sure they are not displaced and remain staggered. Then the sternum is closed. New encircling wires are passed laterally to the longitudinally reinforcing wires in each intercostal space (see Fig 3).

If the patient is large or obese, a double encircling loop of wire could be used at each level so that the sternum is quite stable and firm. The second irrigation-suction system of four tubes is then laid over the sternum and under the skin. The same technique of staggering the chest tubes in the upper and lower half of the sternum is used (Fig 4). All the tubes of the superficial system are brought out through the skin on the left side of the upper abdomen to separate them from the deep system.

Finally, the skin is approximated using monofilament suture in a running or interrupted fashion over the superficial irrigation-suction system. All the irrigation catheters are provided with a three-way stopcock. An antibiotic solution, usually cephalothin at 0.1% concentration, is continuously dripped in each of the irrigation catheters at the rate of 20 mL/h. It is better to have one irrigation bag for each tube, rather than Y-connectors

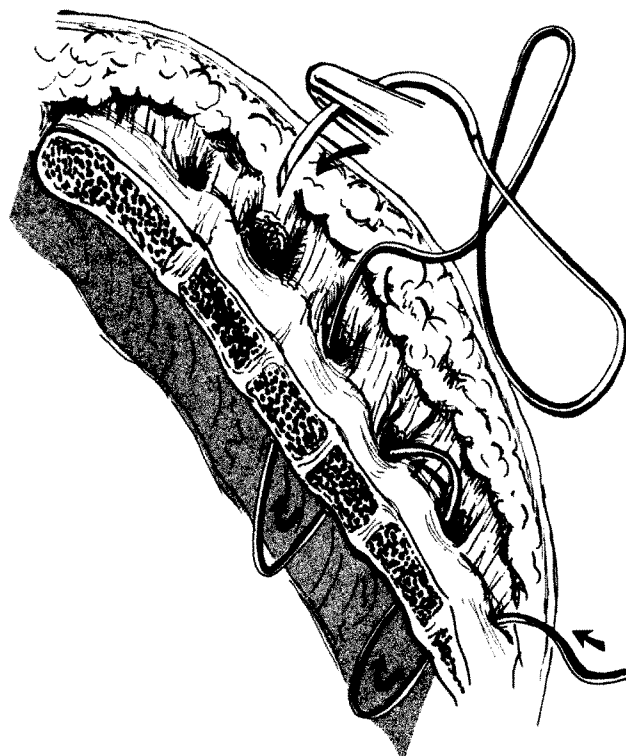


Fig 1. Lateral reinforcement of the sternum is begun at its distal end, passing the wire around the ribs until the manubrium is reached.

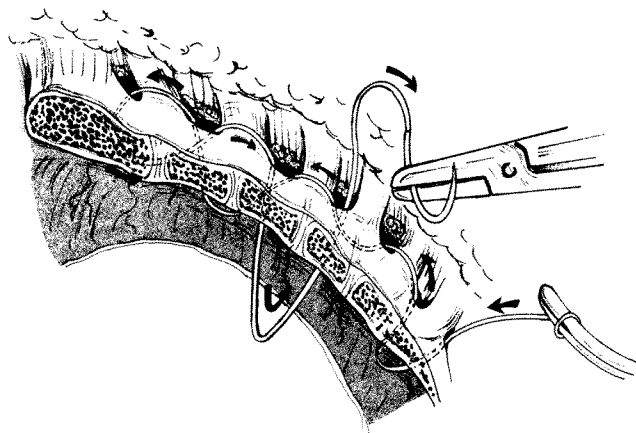


Fig 2. The same wire is brought down, encircling each rib from the opposite side until the distal end is again reached, with the wire twisted and buried.

joining several tubes. This is due to uncertainty over how much of the solution is flowing into each tube.

The suction catheters are connected to a disposable drainage unit, separating the deep system to one unit and the superficial system to a separate unit. The total amount of fluid drained per day is about 1,000 mL per system. Thus, the thoracic drainage (Pleur-evac; Deknatel, Fall River, MA) units are changed every 3 days. If a more economical or convenient suction is preferred, an Emerson large-bottle system (J. H. Emerson, Cambridge, MA) could be used instead.

Length of Treatment

The patient receives intravenous antibiotics every 2 hours during the operation, and then every 6 hours after leaving

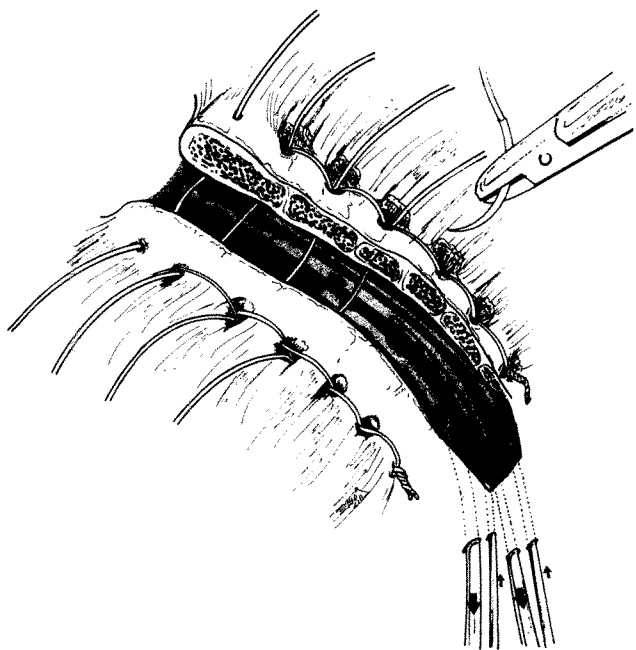


Fig 3. The deep system of irrigating tubes is positioned in a staggered manner, behind the sternum and behind the new encircling sternal wires. All tubes of the deep system are brought out on the right side of the upper abdomen.

the operating room. The operation lasts from 1.5 to 2.5 hours. The irrigation-suction system is enforced without changes or interruptions for 7 days. Even if the return fluid looks clear and the patient is afebrile, it takes 7 days for all the spaces in the mediastinum to fill in until only the tube tracts are present. Therefore, this rule is strictly enforced.

At the end of 7 days, the irrigation is stopped. All irrigation catheters (two superficial and two deep) are removed. The suction catheters are left in exactly the same position; no changes are made for 48 hours. The suction catheters are then gradually advanced every 48 hours over 8 days. In this manner, the tubes are totally removed at the end of 8 days. At that point, administration of the intravenous antibiotic is discontinued, and the patient begins receiving oral antibiotics and is discharged, returning to the outpatient clinic 2 weeks later. The monofilament suture holding the skin edges together is left in place for a total of 2 weeks (occasionally 3 weeks).

At the end of that period, administration of all medications is discontinued. The skin sutures are removed and the patient is followed up at monthly intervals.

Results

Regardless of the time or severity of the infection, I have had no treatment failures, no recurring infections, and no patient deaths throughout my observation period of up to 8 years. None of the patients had to be kept on prolonged respiratory support. The sternum was stable from the time of reoperation. Sternal osteomyelitis did not develop in any of the patients. Hospitalization time varied from 14 to 18 days, and no residual problems have been found.

This method is fully effective in healing infected sternotomy dehiscences. It avoids the use of muscle flap and extensive grafting, shortens hospitalization, and maintains the stability of the chest cage. No reoperations have been required.

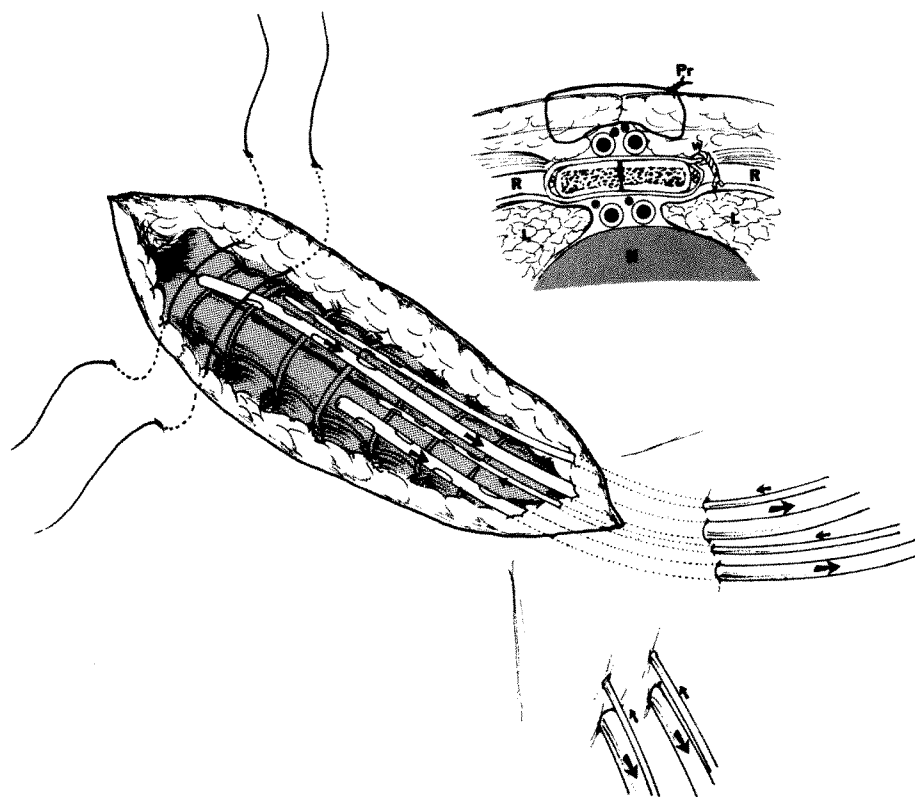
Comment

When infection of the sternotomy incision develops and signs of mediastinitis with sepsis appear, the heart surgeon usually hesitates to attempt another primary closure, and often refers the patient to a plastic surgeon for debridement and repair. The plastic surgeon, on the other hand, usually assumes that all attempts to put the sternum back together are out of the question, and so plans a reconstructive procedure with soft tissues [1, 2, 12, 18, 19].

I firmly believe this is not necessary in most cases, if the technique I describe is used. The question of sternum viability was raised in only 1 of our patients, whose sternum was under a pool of purulent material. A technetium 99m bone scan showed proper uptake. Therefore, I was able to repair the sternum, and the patient healed without any problems.

The first step toward decreasing the rate of sternotomy dehiscence and infection is prevention. When the original sternotomy is made, it must be done properly, in the center, especially if the patient has a weak or unevenly

Fig 4. The sternum is closed with encircling wires placed lateral to the longitudinal reinforcing wires. The superficial suction-irrigation system is laid over the sternum in a staggered manner. Skin and subcutaneous tissue are closed in one layer with monofilament sutures. Insert: A cross section of the repair showing various planes. (H = heart; L = lungs; Pr = Prolene [Ethicon, Somerville, NJ] suture; R = ribs; W = encircling wire around reinforcing wire parallel to sternum.)



shaped sternum, osteoporosis, or soft bone substance. When there is a question of sternal weakness, I have prophylactically used the Robicsek technique [17] described several years ago. I have not experienced any failures using his technique. This prophylactic closure may also be advisable when both internal thoracic arteries have been taken down and the patient fulfills the criteria described by Kouchoukos and associates [9] of high risk for dehiscence; decreased sternal blood flow has been pointed out by Arnold [20] and Palmer and Taylor [21] as a possible factor leading to dehiscence.

The hospital charge for patients with a dehiscent sternum, infected or not, is about 2.8 times greater than for an uncomplicated case [3, 8]. Furthermore, when a plastic surgeon gets involved in repairing this open wound with muscle or skin flaps, the patient is left with an unstable sternum with soft tissue in front of the heart—even if the repair is successful. Hospitalization is prolonged. Reoperation, if needed later, is very difficult. The mortality rate with an infected sternotomy dehiscence ranges from 15% to 50%, and morbidity is also significant. Therefore, whenever the condition is diagnosed, it should be approached aggressively and promptly with an effective technique.

Loop and colleagues [8] recently described four approaches to treat sternal dehiscence. They reported a 17% failure rate with debridement and primary closure, requiring reexploration for sternal instability or persistent sepsis. Previous reports from other authors showed the same problems with this approach. The reason, I believe, is a defectively designed or suboptimally used irrigation-suction system.

A single chest tube, no matter how large, will not work effectively, particularly if multiple holes are made in the tube from the level of the manubrium to the xiphoid. Most commonly, only the bottom holes will stay open, and the upper areas of the sternum will not be treated at all. I contend that placing a single tube is ineffective.

Engelman and co-workers [11] reported a 33% mortality rate using irrigation-suction techniques. The duration of dehiscence in their patients was the same as in mine, from 8 to 42 days. The mediastinal space was drained and irrigated by using only one tube in the retrosternal position and two tubes in the superior mediastinum used for irrigation. They did not laterally reinforce the already weak sternum, and therefore the dehiscence recurred. In their series, several patients were diagnosed too late. No subcutaneous irrigation system was used in any of their patients.

In the cases reported by Bryant and associates [5], the same deficiencies can be found in the irrigation-suction system design. The method described by Shumaker and Mandelbaum [22] suffered the same shortcoming. Cohen and associates [7] also reported failures using a single-tube system. Culliford and colleagues [23] had similar failure rates.

More recently, Ko and associates [24] achieved preliminary success using debridement with closed irrigation. However, the wound in 3 of 14 patients was converted to an open wound and 1 patient died. The irrigating system used was the same type reported by Culliford and colleagues in 1976.

Wray and co-workers [25] treated dehiscence without irrigation. Most of their patients already had osteomyelitis

of the sternum, which implies a late diagnosis. The use of closed mediastinal irrigation reported by Jurkiewicz and associates [12] also had a high failure rate (in 14 of 25 patients), and muscle flaps were subsequently used.

A similar report was made by Majure and colleagues [6] in treating advanced osteomyelitis of the sternum. Scully and associates [2] compared irrigation and closure by mobilizing pectoral muscle versus leaving the incision open and packed for several days before closure; they used povidone-iodine irrigation, which may explain some of the treatment failure with irrigation and closure.

Povidone-iodine has already been proved highly toxic to serosal surfaces, namely peritoneum, by Ahrenholz and Simmons [26]; it is likely to cause the same degree of damage in the pleura and pericardium. In addition, it is highly toxic to the fibroblasts at the concentrations that have bactericidal effects. Povidone-iodine also impairs the chemotaxis of the neutrophils and kills them at the concentration of 1:10 [27]. In addition to these undesirable local effects, povidone-iodine has been reported to be absorbed, causing iodine intoxication and possibly death [28, 29].

Lineaweaver and associates [27] also found that other types of solutions used frequently in wound care (such as hydrogen peroxide at 3% concentration, sodium hypochlorite at 0.5%, or acetic acid at 0.25%), are highly unsuitable due to their tissue toxicity and their ineffectiveness in topically controlled infections. Yet, antibiotic solutions at various concentrations were never found to damage human fibroblasts or neutrophils.

Based on my experience as well as the literature, I agree with Ochsner and associates [14] that muscle flaps and soft tissue should have very limited application in sternotomy dehiscence. After a prompt diagnosis, an aggressive and effective technique must be implemented to simultaneously treat the infection and the dehiscence. The irrigation-suction system I describe, even when applied late, is a very effective first-line approach to combat this complication.

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Effect of Methylprednisolone and Prostacyclin on Bronchial Perfusion in Lung Transplantation

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In an experimental investigation using modified unilateral lung transplantation in pigs, the effects of systemic administration of methylprednisolone and prostacyclin on bronchial mucosal blood flow were assessed. Laser Doppler velocimetry (LDV) and radioisotope studies using radiolabeled erythrocytes (RI) were employed to measure blood flow at the donor main carina and upper lobe carina after 3 hours of reperfusion. The recipient carina was used as a reference point. Five groups of 6 animals each were studied. Group I served as control. In group II, methylprednisolone (20 mg/kg) was administered to the recipient. In group III, prostacyclin ($4 \text{ ng} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) was given to the recipient, and in group IV, prostacyclin (100 μg intravenously) was administered to the donor. In group V, prostacyclin was

given to the recipient and the donor animals as in groups III and IV, respectively. In group I, bronchial blood flow at the donor main carina was $37.6\% \pm 2.2\%$ (LDV) and $44.1\% \pm 14.8\%$ (RI) of reference blood flow. No significant differences were found between the controls and groups II, III, and IV. In group V, bronchial blood flow was markedly increased both at the donor main carina (LDV, $39.8\% \pm 6.2\%$, $p = 0.12$; RI, $55.7\% \pm 11.4\%$, $p < 0.2$) and the donor upper lobe carina (LDV, $65.8\% \pm 5.4\%$, $p < 0.05$; RI, $76.8\% \pm 21.3\%$, $p < 0.2$). We conclude that systemic administration of prostacyclin to the donor and recipient results in marked improvement of bronchial blood flow and may reduce the incidence of bronchial complications after lung transplantation.

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Unilateral and bilateral pulmonary transplantation have become a realistic option for many patients with terminal pulmonary disease and preserved cardiac function [1-4]. Airway complications, however, are still important sequelae of lung transplantation, occurring in 10% to 20% of patients after unilateral and bilateral lung transplantation.

A number of experimental investigations have identified ischemia of the donor bronchus as the most important factor for the occurrence of bronchial complications [5-7]. Deprived of its physiologic blood supply the transplanted airway depends on retrograde perfusion from bronchopulmonary collaterals before bronchial vessels bridge the anastomosis [8, 9]. An omental wrap around the bronchial connection has not been able to uniformly prevent ischemia of the transplanted airways [10]. Direct revascularization of a bronchial artery has been proposed [6, 7, 11, 12]; however, it is technically difficult, it may not be possible in all patients due to variable anatomy of the bronchial vessels [13], and its long-term patency may be questioned [14]. Furthermore, we have previously shown that despite adequate revascularization of a bronchial artery, blood flow may still be subnormal, suggesting a defect in the microcirculation of the transplanted bronchus [15].

We have previously shown in a model of modified unilateral lung transplantation that blood flow at the donor main carina ranges around 35% to 40% of normal airway perfusion [15]. The objective of the present investigation was to verify whether bronchial blood flow can be increased by means of systemic administration of drugs that can be expected to improve the graft microcirculation. Methylprednisolone was chosen for its beneficial effects on leukocyte aggregation and complement activation, possibly limiting reperfusion injury [16]. Prostacyclin has been shown to result in superior postoperative graft function when given to the donor before flushing of the lungs [16]. In addition, prostaglandins appear to play an important role in the regulation of bronchopulmonary collateral blood flow [17, 18]. In this study, the potential effects of these agents were assessed in modified unilateral lung transplantation. Bronchial blood flow was measured using laser Doppler velocimetry (LDV) and radioisotope (RI) studies with radiolabeled erythrocytes.

Material and Methods

Model

The technique of unilateral lung transplantation was modified, leaving the entire left main bronchus, the main carina including the origin of the right main bronchus, and the distal trachea in continuity [1]. The airway anastomosis was performed between the left main bronchus of the recipient and the donor trachea. Left upper lobe carina and main carina of the graft were used to measure

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bronchial blood flow. The recipient carina was chosen as a reference point.

Animals and Anesthesia

Male pigs with a body weight of 20 to 26 kg were used as donor and recipient animals. All animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH publication No. 85-32, revised 1985). The animals were premedicated with azaperone (10 mg/kg intramuscularly), atropine sulfate (0.5 mg intramuscularly), and metomidate hydrochloride (10 mg/kg intravenously) before endotracheal intubation. They were then placed on a respirator (Bennet Respiration Unit MA-1B) with a total volume of 20 mL/kg, a respiratory rate of 15/min, and a positive end-expiratory pressure of 3 cm H₂O. Anesthesia was maintained with 50% oxygen, 50% N₂O, and intravenous injections of fentanyl (0.2 mg), metomidate hydrochloride (200 mg), and pancuronium (4 mg). The respiratory rate was adjusted to achieve an arterial carbon dioxide tension of 35 to 40 mm Hg.

Operative Technique

The operative technique was identical to that published previously [15]. The chest of the donor animal was opened by median sternotomy, and the heart-lung block was prepared for explantation. Heparin (300 U/kg) was given intravenously, and a perfusion catheter was placed in the pulmonary trunk. After inflow occlusion and cross-clamping of the ascending aorta, the tip of the left atrial appendage was amputated and the pulmonary arterial bed perfused with modified Euro-Collins solution, maintaining a pulmonary arterial pressure of 10 to 15 mm Hg [19]. The heart-lung block was then excised. *Ex situ*, the heart and the right lung were removed, and the stump of the right main bronchus was closed with a running suture. Left pulmonary artery and a cuff of left atrial wall surrounding the left pulmonary veins were prepared for implantation. The graft was then placed in cold (4°C) Euro-Collins solution until implantation.

In the recipient animal, a left thoracotomy was performed through the bed of the resected fifth rib. The lung was mobilized, the hemiazygos vein was ligated and divided adjacent to the pulmonary artery, and the pericardium was incised anterior to the pulmonary veins. The left pulmonary artery was occluded at its origin and divided proximal to the first upper lobe branch. The left main bronchus was clamped and divided central to the upper lobe bronchus. Finally, the left atrium adjacent to the pulmonary veins was excluded with a side-biting clamp. The veins were divided and their orifices connected by an incision, creating a common left atrial orifice.

Implantation was begun with an end-to-end anastomosis of donor and recipient left atrium using a continuous everting mattress suture (5-0 Prolene; Ethicon, Somerville, NJ). An end-to-end anastomosis was created between donor and recipient pulmonary artery (5-0 Prolene). The donor trachea was shortened to three rings superior to the main carina, and an end-to-end anastomosis was created between recipient left main bronchus and

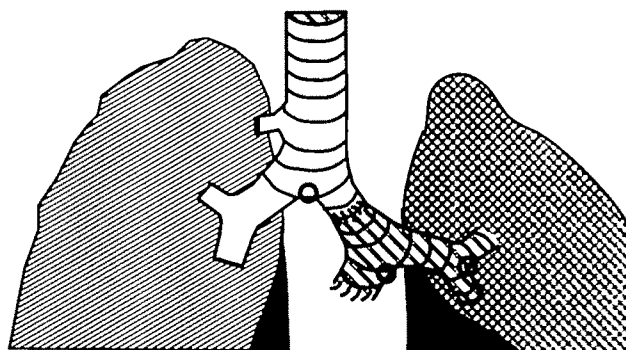


Fig 1. Experimental model: the entire left main bronchus, the main carina including the origin of the right main bronchus, and the distal trachea of the graft (shaded) are left in continuity. The airway anastomosis is performed between the left main bronchus of the recipient and the donor trachea. Bronchial blood flow is assessed at the upper lobe carina and the main carina of the graft (circles); the recipient main carina (circle) is used as reference point.

graft trachea using a running suture (3-0 Prolene). Ventilation was resumed, the pulmonary vascular bed deaired, and the clamps removed.

Measurement of Bronchial Blood Flow

Three hours after reperfusion bronchial mucosal blood flow was measured using LDV (Periflux PF2; Perimed, Stockholm, Sweden). The fiber probe (PF 109 D, Perimed) was introduced through a fiberoptic bronchoscope and guided to the respective measuring points. Under bronchoscopic vision, the laser fiber was placed on the bronchial mucosa, care being taken to obtain a stable signal for at least 10 seconds. This was repeated five times; a mean of these five measurements was calculated and considered as the representative value. Measuring points for each animal were donor main carina and donor upper lobe carina; the recipient main carina was chosen as a reference point (Fig 1). Blood flow was expressed as flow relative to the reference point (donor main carina/recipient main carina, donor upper lobe carina/recipient main carina).

Immediately after completion of the LDV measurements the erythrocytes were labeled *in vivo* using 370 MBq technetium 99m (activation with Technescan PYP; Malinckrodt, Patten, Holland). Fifteen minutes after the injection of technetium 99m, the animal was sacrificed by intravenous injection of T-61 (Hoechst Veterinär, Unterschleissheim, Germany). The central airways of donor and recipient were excised and segments of recipient carina, donor carina, and donor upper lobe carina were removed corresponding to the measuring points of LDV (Fig 2). Radioactivity of the tissue samples was determined in a scintillation chamber and expressed as counts per minute corrected for tissue weight. Relative values were calculated for donor carina and donor upper lobe carina, using the recipient carina as reference.

Experimental Groups

The animals were divided into five groups. Group I ($n = 6$) served as a control group. In group II ($n = 6$) methyl-

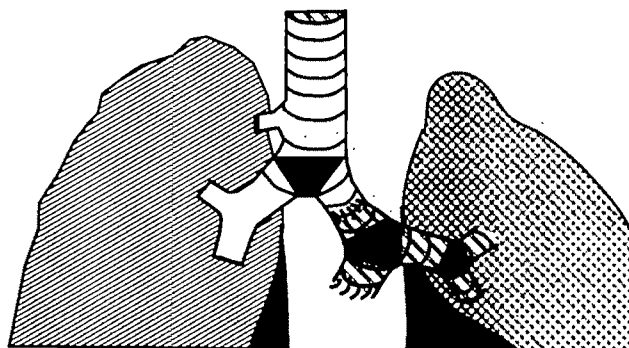


Fig 2. Experimental model: after activation of erythrocytes with technetium 99m, segments of donor and recipient airway (dark areas) are excised for determination of radioactivity.

prednisolone was administered intravenously to the recipient animal 10 minutes before reperfusion (500 mg). In group III ($n = 6$) prostacyclin was given as a continuous intravenous infusion ($4 \text{ ng} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$), beginning 10 minutes before reperfusion and continuing throughout the observation period. In group IV ($n = 6$) prostacyclin ($100 \mu\text{g}$) was given intravenously to the donor animal before the Euro-Collins flush. In group V ($n = 6$) prostacyclin ($100 \mu\text{g}$ intravenously) was administered to the donor animal and given as a constant infusion ($4 \text{ ng} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) to the recipient animal.

Statistical Methods

Mean values $\pm$ standard deviations were calculated. Statistical comparison between the groups was performed using analysis of variance. A p value of less than 0.05 was considered significant.

Results

Body weight of the experimental animals and hemodynamic data obtained after 3 hours of reperfusion are depicted in Table 1. There was no significant difference between the groups with respect to body weight; therefore, cardiac output measurements were not indexed by the animals' weight. Mean arterial pressure was significantly lower in group III compared with groups I, IV, and V ($p < 0.05$). Concurrently, pulmonary artery pressures were lower in group III than in groups IV and V ($p <$

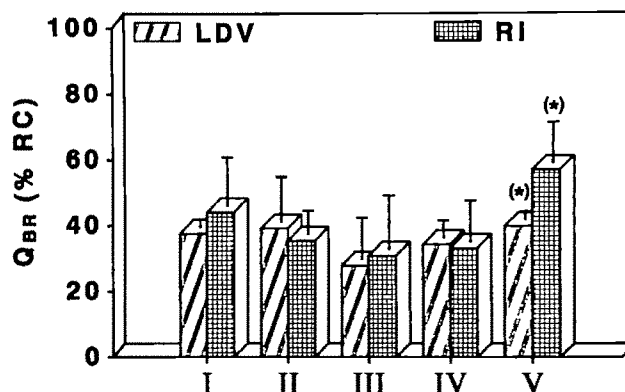


Fig 3. Bronchial blood flow (Q_{BR}) at donor main carina. Both by laser Doppler (LDV) and radioisotope (RI) studies, an increase in bronchial blood flow is observed only in group V (prostacyclin to donor and recipient). Due to group variability, the differences are not statistically significant [$(*) = p < 0.2$]. (RC = recipient main carina.)

0.05). In group IV, cardiac output was significantly higher than in groups II and III. No significant differences existed between groups I and V with respect to any of the parameters measured.

Three hours postoperatively bronchial blood flow at the donor main carina was markedly decreased in group I (LDV, $37.6\% \pm 2.2\%$; RI, $44.1\% \pm 14.8\%$). In groups II (LDV, $29.2\% \pm 13.5\%$; RI, $35.4\% \pm 7.0\%$), III (LDV, $27.8\% \pm 12.4\%$; RI, $30.8\% \pm 16.2\%$), and IV (LDV, $34.3\% \pm 5.1\%$; RI, $33.1\% \pm 12.3\%$) blood flow at the donor carina was unchanged compared with group I (Fig 3). In group V an increase in bronchial blood flow was observed (LDV, $39.8\% \pm 2.4\%$, $p = 0.12$; RI, $57.1\% \pm 12.3\%$, $p = 0.14$). The increase was not statistically significant due to interindividual variability.

At the donor upper lobe carina, subnormal blood flow also was found in the control group (LDV, $54.9\% \pm 7.7\%$; RI, $61.6\% \pm 25.7\%$). Flow at the upper lobe carina did not show a significant difference between the control group and groups II (LDV, $62.0\% \pm 5.9\%$; RI, $44.0\% \pm 8.1\%$), III (LDV, $58.1\% \pm 3.7\%$; RI, $59.2\% \pm 19.8\%$), and IV (LDV, $57.6\% \pm 5.9\%$; RI, $64.3\% \pm 18.1\%$) (Fig 4). In group V, blood flow was significantly improved compared with the control group (LDV, $66.1\% \pm 5.9\%$; RI, $80.3\% \pm 21.8\%$, $p < 0.05$).

Comment

Airway complications were one of the main causes of death in the early experience with lung transplantation [6, 20]. A number of experimental and clinical observations have indicated that bronchial ischemia is the most important factor responsible for the occurrence of these sequelae of lung transplantation [6, 7, 15]. After transplantation, the grafted bronchus is deprived of its physiologic arterial blood supply and for a period of 3 to 4 weeks depends on retrograde blood flow from bronchopulmonary collaterals [8, 9].

A number of experimental approaches have been suggested to avoid bronchial ischemia. Minimizing dissection

Table 1. Variables Measured in the Five Experimental Groups After Three Hours of Reperfusion

Group	BW (kg)	MAP (mm Hg)	PAP (mm Hg)	CO (L/min)
I	24.5 $\pm$ 1.9	60.8 $\pm$ 9.2	22.7 $\pm$ 11.0	2.6 $\pm$ 0.6
II	23.3 $\pm$ 2.6	56.7 $\pm$ 8.0	19.8 $\pm$ 7.3	2.0 $\pm$ 0.5
III	22.5 $\pm$ 1.7	52.3 $\pm$ 7.3	13.0 $\pm$ 2.9	1.7 $\pm$ 0.6
IV	24.1 $\pm$ 1.9	62.4 $\pm$ 10.2	19.1 $\pm$ 2.5	2.8 $\pm$ 0.8
V	22.2 $\pm$ 2.8	61.8 $\pm$ 9.6	17.5 $\pm$ 4.7	2.5 $\pm$ 0.7

BW = body weight; CO = cardiac output; MAP = mean arterial pressure; PAP = pulmonary artery pressure.

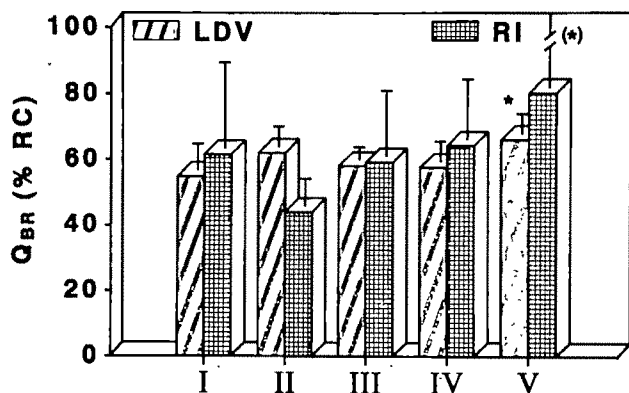


Fig 4. Bronchial blood flow (Q_{BR}) at the graft upper lobe carina. Both laser Doppler (LDV) and radioisotope (RI) studies demonstrate a marked increase in blood flow only in group V (prostacyclin to donor and recipient). As measured by LDV, the difference is significant (* $p < 0.05$); due to group variability, RI did not show a significant increase [(*) = $p < 0.2$]. (RC = recipient main carina.)

around the donor airway [5], choosing an anastomotic site as peripheral as possible on the graft airway [21, 22], using an omental wrap [23], and revascularization of a bronchial artery [6, 7] have been found to reduce the prevalence and severity of bronchial complications in experimental lung transplantation.

The concept of using bronchial omentopexy was introduced into clinical lung transplantation [4, 14]. It was thought that the success of unilateral as well as bilateral lung transplantation could be attributed to the use of the omentum [4]. With increasing experience, however, it became apparent that airway complications still occurred in more than 10% of the patients [10]. Clinical observations indicated that bronchial stenoses were preceded by bronchoscopic evidence of ischemia in the graft airway. These ischemic changes are commonly apparent within the first postoperative week, indicating either inadequate ingrowth of collateral vessels from the omentum or inadequate collateral blood supply.

Direct revascularization of a bronchial artery has been performed experimentally and clinically [6, 11, 12, 14, 22] and results in significant improvement in bronchial mucosal blood flow [15]. Normalization of bronchial blood flow, however, could not be achieved, indicating a possible defect in the microcirculation of the graft [15]. In addition, revascularization of a bronchial artery may be technically difficult and may not always be feasible due to the variable anatomy of the bronchial vessels [13]. Up to now, few investigations have focused on preservation of bronchial or pulmonary microcirculation or improvement of bronchopulmonary collateral flow as an alternative source of bronchial blood supply after transplantation.

The present model was chosen to imitate the clinical situation, in which the graft undergoes the surgical trauma of transplantation and the pulmonary vascular bed is perfused by pulsatile blood flow. The length of the transplanted airway was extended intentionally to provide information on blood flow in the left main bronchus; because in clinical transplantation the airway anastomosis

is performed at this level, information on perfusion of the airway central to the upper lobe bronchus was considered to be of clinical relevance. In addition, investigations on blood flow at the level of the upper lobe carina have demonstrated little difference between normal levels and those achieved after transplantation [24]. Measurement of blood flow using LDV requires placement of the endoscopic probe orthogonal to the surface of the bronchus, making main carina and lobe carinas the only practical measuring points. For this reason, blood flow cannot be measured along the left main bronchus in a position where an anastomosis is placed under normal clinical conditions. Blood flow along the left main bronchus can, however, be extrapolated from proximal and distal measuring points.

Laser Doppler velocimetry was employed as one method for measuring bronchial mucosal blood flow; its value in assessment of blood flow of bronchial mucosa has been documented [5, 25]. A drawback of the system is its inability to measure absolute blood flow. In addition, changes in the pressure with which the endoscopic fiber is held onto the surface may alter the results. Attempts were made to minimize these drawbacks. The use of a reference point (recipient main carina) allowed for determination of relative values without the need for correcting factors between individual experiments. To minimize the effect of airway movements on the results, a stable signal was obtained for at least 10 seconds. The measurements were repeated five times, and the mean value was accepted for analysis. The small interindividual variability within each experimental group indicates that the technique of LDV was used correctly.

The use of radioactive microspheres is an accepted method in assessing relative bronchial blood flow [18, 26]. In this investigation, however, the blood flow to be measured was to pass the pulmonary vascular bed and bronchopulmonary collaterals before entering the bronchial vascular bed. Therefore, it was uncertain whether microspheres at defined diameters would be able to pass the collateral vessels rather than embolizing in the pulmonary capillaries. Thus, labeled erythrocytes were chosen as "microspheres," assuming that they would represent the most reliable indicator of true bronchopulmonary collateral flow to the transplanted airway in the present model. The good correlation between values obtained by LDV and RI indicates that—despite the modification in radioisotope tracers—acceptable data were obtained by RI.

Prostacyclin is a natural prostaglandin with strong vasodilating action on the pulmonary as well as the peripheral arterial bed [27, 28]. Its effect with regard to inhibition of platelet aggregation has been used to decrease platelet consumption during cardiopulmonary bypass and hemodialysis [29]. In experimental pulmonary transplantation, prostacyclin has been found to improve preservation when given to the organ donor before Euro-Collins flush [30]. Corticosteroids can be expected to exhibit a positive effect on graft microcirculation by limiting vascular injury via inhibition of proteolytic enzyme release from polymorphonuclear leukocytes, decreased

platelet and leukocyte aggregation, and increased membrane stability [31].

The results obtained in the control group confirmed that after transplantation perfusion of the transplanted bronchus is subnormal. Compared with the physiologic situation, the central airway receives approximately 35% of its normal blood supply. In addition, the blood derived from bronchopulmonary collaterals is of limited oxygenation, possibly resulting in decreased tissue oxygen tension below critical levels required for survival of tissue and adequate healing. No improved bronchial blood flow was observed after administration of methylprednisolone. This may be due to the fact that the dose employed (20 mg/kg) was relatively small compared with the dose employed in shock (40 mg/kg) [31]. On the other hand, it may also indicate that despite its positive actions on the mechanisms involved in reperfusion injury, the duration of postoperative follow-up or the timing of administration were inadequate to demonstrate a positive effect [31]. Finally, a type 2 error may have prevented detection of differences between groups I and II.

After administration of prostacyclin either to the donor or the recipient animal, no improvement in bronchial blood flow was observed. With combined administration of prostacyclin both to donor and recipient, however, a marked improvement in bronchial blood flow was observed. The level of blood flow was similar to that obtained by direct revascularization of a bronchial artery in a previous investigation [15]. Because no significant difference in the hemodynamic variables measured in groups I and V were observed, this increase in blood flow is unlikely due to general hemodynamic effects of prostacyclin. Rather, an intrapulmonary mode of action, such as increased bronchopulmonary collateral flow, must be assumed. The decrease in blood flow in group III in conjunction with lower pulmonary artery pressures and cardiac output, however, indicate that hemodynamic variables may exert an influence on bronchial blood flow. Relative hypovolemia, which can be assumed according to the hemodynamic data, may result in inadequate bronchial perfusion. Conclusions drawn from this investigation have to be limited due to the low number of experimental investigations in each group. Since completion of the experiments, we have modified our clinical regimen, including combined administration of prostacyclin to donor and recipient. Concurrent with the change in the therapeutic regimen, a decrease in the incidence of bronchial complications has been observed [32].

The results obtained previously [15] indicate that the occurrence of bronchial ischemia may in part be caused by a defect in the graft microcirculation. Little is known about the mechanisms of this defect, because research in pulmonary preservation has mainly focused on graft function with respect to gas exchange. Little information is available on the effects of ischemia and the current preservation methods on the pulmonary vascular compartment. Experimental observations and the experience from renal and hepatic transplantation indicate that the high potassium concentration of Euro-Collins solution may lead to significant vasospasm of the perfused vascular bed.

The improvement in pulmonary graft function after administration of prostacyclin before the Euro-Collins flush may in part be mediated by inhibition of vasospasm and consequent avoidance of inhomogeneous perfusion. Experimental observations also suggest that the endothelial cells may show signs of temporary damage after Euro-Collins flush perfusion and extraction (unpublished data). Inadequate perfusion of the bronchial vascular bed during pulmonary artery flush has been suggested as a possible mechanism of inadequate pulmonary preservation [33]. Using the identical model, we added flush perfusion of the descending thoracic aorta to the pulmonary artery flush and obtained results identical to the control group (unpublished data). Thus, inadequate perfusion and preservation of the bronchial arteries does not appear to be a probable mechanism responsible for the defect in microcirculation. Improved pulmonary preservation may further control the problem of bronchial ischemia after pulmonary transplantation.

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Pressure–Volume Relationship of the Fetal Lamb Heart

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In contrast to the adult heart, the fetal heart reportedly has little functional reserve. With increased clinical emphasis on fetal cardiac diagnosis, neonatal surgery, and the potential for future fetal cardiac intervention, it is essential that we better understand fetal cardiac function. Therefore, to demonstrate the extent of fetal cardiac preload reserve, we studied 10 fetal lambs using an isolated, isovolumic, blood-perfused heart preparation. We maintained constant afterload, inotropic state, coronary blood flow, heart rate, and perfusate blood gas values. As left ventricular (LV) volume (preload) was incrementally increased, LV end-diastolic pressure and

LV peak systolic pressure were recorded. Linear regression analysis demonstrated that increases in LV developed pressures were predicted by the LV volume, demonstrating the presence of the Frank-Starling mechanism in each case. The plateau of the Starling pressure–volume curve occurred at an LV end-diastolic pressure of 12.5 ± 4.79 mm Hg (95% confidence interval, 9.07 to 15.9 mm Hg), lower than the plateau expected in the adult heart. This implies that, in the management of fetal and immature neonatal hearts, preload reserve plays an important but limited role in cardiac reserve.

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Increasing attention is being paid to the clinical aspects of fetal cardiac development, congenital defects, and fetal cardiac function [1, 2]. Recent advances in noncardiac fetal surgery [3–6] have suggested the feasibility and possible advantages of fetal surgical intervention for certain lesions. It is likely that selective fetal intervention for congenital heart lesions will also be beneficial. If we are to properly interpret prenatal cardiac diagnosis and consider managing the fetus surgically, it will be essential to understand fetal cardiac mechanics and the mechanisms we can recruit to optimize fetal cardiac function. In addition, the understanding of fetal cardiac mechanics will help us in the care of neonates in whom cardiac mechanics is in transition between the immature and mature states.

Cardiac preload reserve defines the role of the active length–tension mechanism, or Frank-Starling pressure–volume curve, of the heart. It represents the capacity to increase cardiac output from baseline by increasing preload or cardiac end-diastolic volume. Although many studies have demonstrated little or no preload reserve in fetal myocardium, especially when compared with mature myocardium [7–13], others have demonstrated significant preload reserve in the fetal heart [14–16]. The discrepancy of these results may be secondary to the difficulty in studying the fetal heart. Exteriorized fetal preparations are intrinsically unstable [17]. Although more stable, chronic in utero preparations are difficult to

study because of the investigators' inability to isolate and independently control the major variable determinants of cardiac function: preload, afterload, inotropic state, coronary blood flow, and heart rate.

This study was designed to evaluate the extent of cardiac preload reserve in the fetus using a modified isolated, isovolumic fetal lamb heart preparation. The model developed is stable and allowed us to independently control variables of cardiac function including preload, afterload, heart rate, and coronary perfusion pressure. In addition, this preparation removes inotropic state and hormonal and neural influences on cardiac mechanics.

Material and Methods

Fetal cardiac mechanics were studied in 10 fetal lambs of 129 to 135 days gestational age (term gestation = 145 to 155 days) to determine the fetal capacity for cardiac preload reserve and to establish the stability of our model.

Animal Preparation

This study was performed using protocols approved by the Institutional Animal Use and Care Protocol Committee of Temple University Medical School. By using a ewe carrying a twin gestation, it was possible to have an ideal donor for blood and two experimental animals. Each pregnant ewe was sedated with ketamine (10 mg/kg intravenously), intubated, maintained on a volume ventilator, and anesthetized with a gas mixture of 30% oxygen and 70% nitrous oxide augmented with continuous intravenous infusion of fentanyl. This anesthetized the fetuses as well as the ewe and avoided the reduction

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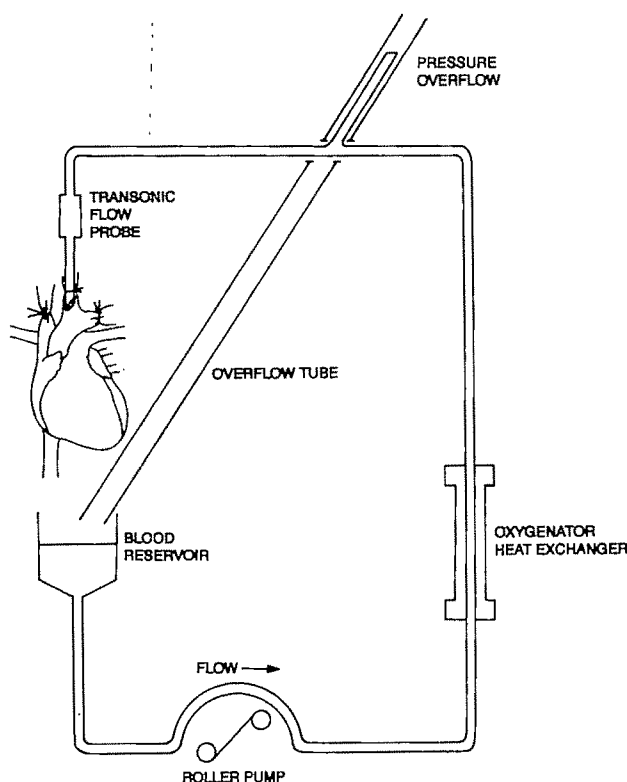


Fig 1. Circuitry of isolated heart preparation.

in inotropic state caused by anesthetics such as halothane or pentobarbital. The ewe was anticoagulated with $3 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ heparin intravenously. The fetal lamb was delivered through a right-sided laparotomy and small hysterotomy, taking care to avoid umbilical cord compression. A fetal median sternotomy was performed, the pericardium opened, the heart exposed, and the fetal innominate artery cannulated with an 8F perfusion cannula. Simultaneously, the ewe's right carotid artery was cannulated to drain 500 mL of maternal blood to prime the isolated perfusion system described below. The fetal inferior and superior venae cavae were divided. When the fetal aortic pressure dropped to 10 to 20 mm Hg, the aortic arch distal to the innominate artery was ligated and the isolated perfusion system instituted, perfusing the fetal aortic root and coronary arteries.

Isolated Heart Preparation

The perfusion system was a closed-loop system consisting of a venous reservoir, heat exchanger, membrane oxygenator (Scimed Life Systems Inc), and a roller pump (Masterflex, N-07520-35) designed to perfuse the fetal heart at 50 mm Hg (Fig 1). The perfusion pump was servo-computer controlled to maintain the chosen constant coronary perfusion pressure of 50 mm Hg, mimicking the in utero systolic pressure, by using the digitized aortic root pressure to continually adjust the Masterflex pump output. In three experiments, constant coronary perfusion pressure was maintained using an elevated arterial line overflow reservoir. Coronary venous and thebesian blood was drained by gravity to the venous reservoir.

After excision of the fetal heart, the fetal blood was collected in a second blood reservoir. When the isolated preparation was stable, the fetal blood was substituted in the circuit for the maternal blood to avoid any effects of adult hemoglobin with its oxygen dissociation curve shifted to the right compared with fetal blood.

Side ports on the perfusion circuit provided for measurement and recording of fetal coronary artery pressure and temperature, and periodic sampling of oxygen tension, carbon dioxide tension, and pH.

A latex elliptical balloon mounted on a 5F single-lumen Millar catheter was inserted into the cavity of the left ventricle through a left atriotomy. It was positioned by a plastic ring on the balloon catheter secured to a mitral annulus pursestring suture. The balloon had an unstressed volume of 6 to 8 mL, much larger than the largest left ventricular (LV) volume. At the completion of each experiment, the left ventricle was dissected with the balloon in place, confirming that the balloon "fit" the ventricle well. The LV apex was vented to drain thebesian flow and decompress the left ventricle of blood. Two epicardial pacing wires were placed on the right ventricular free wall, and the heart was paced at a fixed rate of 180 beats/min.

Determination of Left Ventricular Systolic and Diastolic Pressure-Volume Relationships

Preload was varied in a controlled manner by gradually increasing the LV balloon volume. This was accomplished by increasing the balloon volume by increments of 0.1 or 0.2 mL from V_0 (defined as the volume at which LV end-diastolic pressure [LVEDP] was 0) until no further increment in developed pressure occurred. At balloon volumes near V_0 , small increments in balloon volume changed the LVEDP; thus V_0 was easy to define. At each balloon volume the heart was allowed to stabilize for at least 3 minutes and the LVEDP, LV peak systolic pressure (LVSP), LV developed pressure (LVDP), coronary blood flow, and coronary perfusion pressure were recorded. Increases in LVEDP and LVSP were measured by continuous recording from the Millar catheter in the balloon. Left ventricular developed pressure was calculated at each balloon volume using the equation: $\text{LVDP} = \text{LVSP} - \text{LVEDP}$.

Pressure-volume curves were generated for each fetal heart by plotting balloon volume (corrected for the deflated balloon volume) against LVEDP, LVSP, and LVDP. Dependence of LVDP on LV volume was analyzed by performing linear regression analysis of the LV volume (independent variable) and LVDP (dependent variable) throughout the range of LV volumes from an LVEDP of 0 to the LV volume at which the LVDP reached its plateau.

Results

The long-term stability of this preparation was confirmed in two preparations in which the LV balloon volume, heart rate, and coronary perfusion pressure were held constant for 1 hour. Serial measurements of LVEDP,

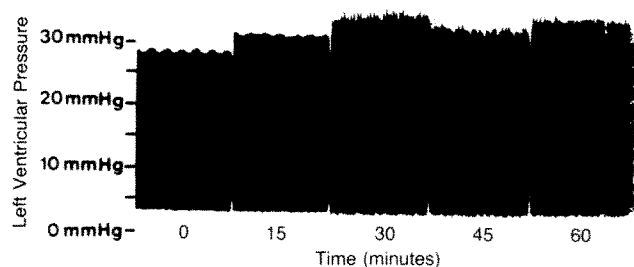


Fig 2. Serial left ventricular pressure recording from an isolated fetal heart at a constant ventricular balloon volume recorded at 15-minute intervals over 1 hour. Minimal variation in left ventricular end-diastolic pressure and left ventricular developed pressure demonstrates stability of the preparation.

LVDP, LVSP, and coronary blood flow demonstrated minimal variation (Fig 2).

After each increment in corrected end-diastolic volume, LVSP stabilized within 10 beats. Consistent pressure-volume function relations (Starling curves) were obtained from each fetal heart preparation (Table 1, Fig 3). As LV end-diastolic volume and, therefore, preload, was increased, there was a clear increase in developed pressure until an LVDP plateau was reached, demonstrating the presence of the Starling mechanism, or preload reserve. For each pair of data, linear regression analysis of corrected LV volume (independent variable) and LVDP (dependent variable) consistently demonstrated a statistically significant positive relationship (Table 2). In each case, the linear regression curve defined a line with a positive slope ($176 \pm 75.54 \text{ mm Hg} \cdot \text{mL}^{-1} \cdot \text{g LV weight}^{-1}$). This was highly significant as demonstrated by r^2 and F values (see Table 2) in each case. Linear regression defined a better fit to the data than second- and third-degree curves in each animal.

The plateau of the Starling curve occurred at an LVEDP mean of $12.5 \pm 4.79 \text{ mm Hg}$, with a range from 7 to 22 mm Hg (see Table 1). The 95% confidence limit of LVEDP at the Starling curve plateau was 9.07 to 15.9 mm Hg.

Comment

As we increasingly incorporate fetal diagnosis of cardiac defects into our clinical armamentarium, an understanding of fetal cardiac mechanics will become essential. Basic to our understanding of adult cardiac function is the role of preload reserve, the active length-tension relationship described by Frank and Starling. Preload reserve is of comparable importance for the fetus as it responds to altered cardiac demand associated with stresses such as growth, hypoxia, infections, the birth process, and congenital cardiac lesions. With increasing use of fetal therapy and manipulation, the clinician will have to be able to recruit this reserve when augmentation of fetal cardiac output is indicated. In addition, neonatal cardiac mechanics, especially in the premature neonate, represents a transitional state between fetal and mature cardiac mechanics.

The structural and biochemical characteristics of the

Table 1. Hemodynamic Data of Isolated Neonatal Hearts^a

Ewe No.	EDP (mm Hg)	PK PR (mm Hg)	DEV PR (mm Hg)	NORM VOL (mL/g)
1	6	44	38	0.08
	7	60	53	0.13
	7	71	64	0.19
	8	79	71	0.23
	10	92	82	0.28
	12	101	89	0.33
	15	103	88	0.37
	21	104	83	0.42
2	2	21	19	0.23
	3	24	21	0.32
	3	28	25	0.41
	3	37	34	0.50
	4	55	51	0.59
	7	70	63	0.68
	13	79	66	0.77
	21	80	59	0.82
3	1	22	21	0.09
	2	35	33	0.11
	4	35	31	0.13
	4	52	48	0.15
	6	73	67	0.17
	6	70	64	0.19
	6	77	71	0.21
	7	83	76	0.22
	7	89	82	0.24
	7	96	89	0.26
	7	101	94	0.28
4	8	106	98	0.30
	8	111	103	0.32
	9	119	110	0.34
	9	120	111	0.36
	10	118	108	0.38
	11	122	111	0.40
	-1	8	9	0.11
	-2	9	11	0.11
	0	10	10	0.13
	-1	11	12	0.14
	1	14	13	0.16
	2	16	14	0.18
	0	20	20	0.19
	3	24	21	0.21
	4	27	23	0.23
	5	31	26	0.24
	5	34	29	0.26
	7	38	31	0.28
	7	44	37	0.29
	9	48	39	0.31
	10	53	43	0.33
	14	57	43	0.34
	14	59	45	0.35
	15	60	45	0.36
	19	65	46	0.38
	22	69	47	0.39
	17	65	48	0.39
	20	67	47	0.38
	21	69	48	0.39

Table 1. Continued

Ewe No.	EDP (mm Hg)	PK PR (mm Hg)	DEV PR (mm Hg)	NORM VOL (mL/g)
5	22	71	49	0.40
	23	73	50	0.41
	28	76	48	0.42
	-1	12	13	0.18
	1	19	18	0.22
	4	27	23	0.26
	5	32	27	0.31
	9	37	28	0.35
	9	37	28	0.37
	11	39	28	0.39
6	0	44	44	0.15
	0	52	52	0.18
	4	60	56	0.21
	3	61	58	0.22
	4	73	69	0.25
	4	77	73	0.27
	6	77	71	0.30
	7	84	77	0.32
	8	85	77	0.35
	7	88	81	0.37
7	11	91	80	0.40
	11	92	81	0.43
	14	95	81	0.45
	16	95	79	0.48
	-2	11	13	0.05
	0	21	21	0.08
	1	29	28	0.10
	2	36	34	0.12
	2	42	40	0.14
	3	47	44	0.15
8	4	50	46	0.17
	4	56	52	0.19
	6	62	56	0.21
	6	67	61	0.22
	7	66	59	0.24
	9	65	56	0.26
	11	69	58	0.27
	13	73	60	0.29
	0	16	16	0.14
	1	22	21	0.15
9	3	27	24	0.17
	5	31	26	0.19
	8	37	29	0.21
	10	41	31	0.22
	12	46	34	0.26
	15	52	37	0.27
	17	56	39	0.29
	19	61	42	0.31
	24	65	41	0.32
	0	12	12	0.11
	-1	14	15	0.12
	2	16	14	0.14
	2	19	17	0.16
	4	23	19	0.17
	5	27	22	0.19
	4	31	27	0.21

Table 1. Continued

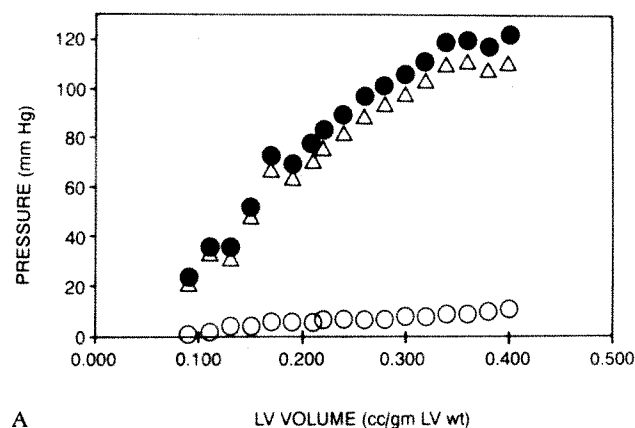
Ewe No.	EDP (mm Hg)	PK PR (mm Hg)	DEV PR (mm Hg)	NORM VOL (mL/g)
	7	37	30	0.22
	7	40	33	0.24
	10	46	36	0.26
	11	52	41	0.27
	14	57	43	0.29
	16	61	45	0.31
	19	66	47	0.32
	22	70	48	0.34
	27	75	48	0.36
	30	80	50	0.37
10	35	82	47	0.39
	0	22	22	0.20
	2	31	29	0.24
	4	39	35	0.28
	8	47	40	0.31
	12	52	40	0.35
	15	54	39	0.37

* These data were used to generate the Starling curves in Figure 3.

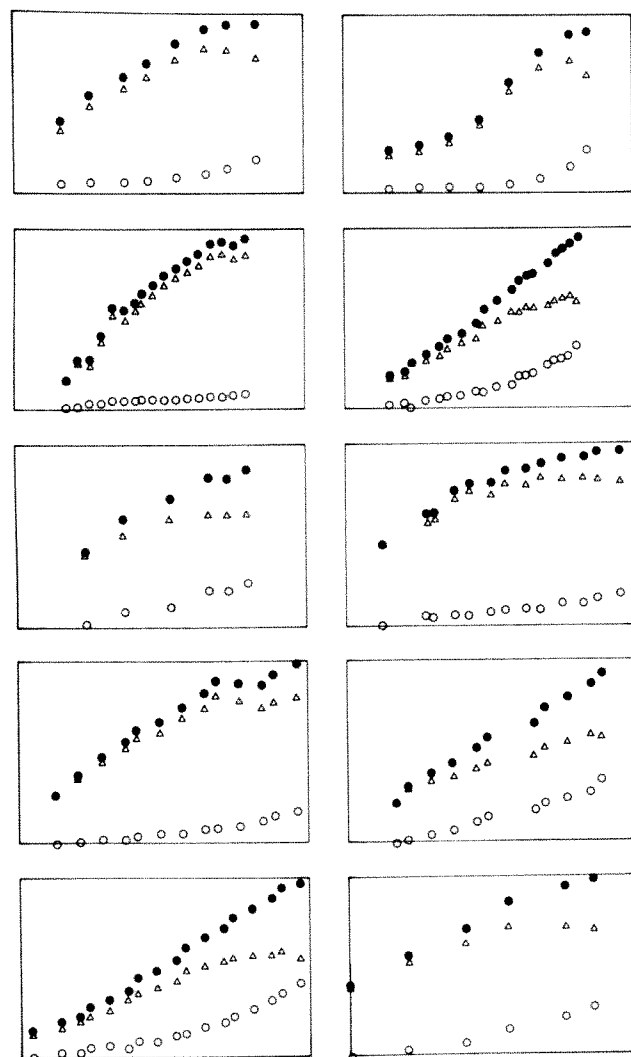
EDP = end-diastolic pressure; DEV PR = developed pressure (PK PR - EDP); NORM VOL = left ventricular (LV) volume normalized for LV weight = LVB balloon volume/LV weight (where LV weight = weight of LV free wall + 1/2 septum); PK PR = peak systolic pressure.

fetal heart change throughout gestation. As normal development progresses in the embryo and fetus, many changes occur in structure and biochemical properties, including increases in the numbers and cross-sectional area of cardiac myocytes, increases in myofibrillar density, development of transverse tubules, development of sarcoplasmic reticulum, growth of the coronary arteries, an increase in myosin adenosine triphosphate activity, a change in myofilament sensitivity to calcium, and a decrease in glycogen level [18-20]. Although these changes in structural and biochemical properties strongly suggest that there are major alterations in mechanical function associated with normal development, we know of no studies that have correlated these structural changes with preload, afterload, and functional mechanics in the fetal heart.

In contrast to the adult heart, the fetal heart has been reported to have little functional reserve. Rudolph and others have suggested that increases in preload produce little or no increase in cardiac output [7-13]. Others, however, have demonstrated the length-tension response both in isolated muscle strip preparations and in the intact fetus [14-16, 21]. In our experiment, the Starling curve peaked at an LVEDP of 7 to 22 mm Hg (95% confidence interval, 9.07 to 15.9 mm Hg), which correlates well with the data of Kirkpatrick and associates [14], who found that the developed pressure peaked at an LVEDP of about 10 mm Hg. The lack of preload reserve found by some investigators may be explained by the fact that the resting LVEDP of the fetal heart is close to the LVEDP that produces peak LVDP. Thus, although the fetal heart exhibits a clear Starling mechanism, it may be unable to recruit reserve function because it functions near the peak of the curve at rest.



A



B

Fig 3. (A) Representative pressure-volume curve from fetal heart 3. (B) Starling curves from each of the 10 isolated fetal hearts. (Closed circles = left ventricular peak pressure; open circles = left ventricular end-diastolic pressure; open triangles = left ventricular developed pressure.)

It is not surprising that the fetal heart works at rest near peak function because the cardiac demands are ever-increasing in the rapidly growing fetus. Indeed, it may be

Table 2. Linear Regression Curves for Pressure-Volume Relationship of the Fetal Left Ventricle^a

Fetus No.	Y-Intercept Constant (a)	Slope Variable (b)	Linear Equation	Correlation	r ² Value	F Value	Intercept (a)		Slope (b)	
							t Value	Hypothesis Significant ^b	t Value	Hypothesis Significant ^b
1	24.48 (10.34)	202.92	DP = 24.48 + 202.92 × Vol	0.993663	0.987366	312.620	9.61061 (1.74670)	Yes	17.68102	Yes
2		99.50	DP = -10.34 + 99.50 × Vol	0.970509	0.941887	81.046		No	9.00226	Yes
3		328.54	DP = -10.34 + 328.54 × Vol	0.981146	0.962647	355.038		Yes	18.30403	Yes
4	(8.13)	144.95	DP = -8.13 + 144.95 × Vol	0.992987	0.986038	1622.705	(7.62936)	Yes	40.28281	Yes
5	(1.60)	88.92	DP = -1.60 + 88.92 × Vol	0.978676	0.957808	68.104	(0.54922)	No	8.25254	Yes
6	23.07 (0.49)	163.12	DP = 23.07 + 163.12 × Vol	0.960315	0.922205	94.835	5.08284 (0.41453)	Yes	9.73833	Yes
7		279.36	DP = -0.49 + 279.36 × Vol	0.996893	0.993796	1281.601		No	35.79946	Yes
8	(0.65)	138.54	DP = -0.65 + 138.54 × Vol	0.991805	0.983678	482.149	(0.45270)	No	21.95788	Yes
9	(5.89)	158.96	DP = -5.89 + 158.96 × Vol	0.987785	0.975720	602.811	(3.59431)	Yes	24.55220	Yes
10	(8.36)	155.26	DP = -8.36 + 155.26 × Vol	0.997866	0.995737	467.209	(4.48075)	Yes	21.61502	Yes

^a The pressure-volume data are fitted to the "best-fit" linear equation. The equation is in the form: DP = a + b × Vol, where DP = left ventricular developed pressure, Vol = normalized left ventricular volume (mL/g of left ventricular weight), a = Y intercept constant, and b = slope. ^b Hypothesis is tested at 95% confidence limit (Yes = significant).

that the wall stress associated with working at the peak of the Starling curve may be a primary stimulus of fetal cardiac growth in response to body growth. We have no explanation for the low LVEDP for peak LV function in the fetal heart compared with the mature heart. It cannot be explained by compliance, because the fetal heart is less compliant than the mature heart [22, 23]. Thus we would expect the less compliant fetal heart to demonstrate a higher LVEDP at the LVDP plateau rather than the lower LVEDP we have demonstrated. Other explanations may include (1) differences between fetal and mature myocardium as discussed above, (2) differences in fetal and mature coronary circulation, or (3) differences in inotropic state.

The isolated adult heart has been used widely to study cardiac metabolism and mechanics [21]. Our model employs the fetal lamb heart in an isolated isovolumetrically contracting model employing completely extracorporeal circuitry and autologous fetal blood. With this model, we were able to study a stable fetal working heart, controlling variables of cardiac mechanics such as heart rate, afterload, coronary perfusion pressure, and inotropic state while evaluating the LV volume-pressure relationship.

In summary, we have used a beating isolated heart model to study fetal cardiac mechanics. We have demonstrated in this study that the fetal lamb heart is capable of a significant systolic pressure-volume relationship. This is demonstrated by the Starling curves consistently produced, and is confirmed by the regression analysis that demonstrates a clear relationship between preload (LV volume in this study) and LVDP. The Starling curve consistently peaks at a lower end-diastolic pressure than has been reported for mature or adult hearts. However, the mechanism to explain this is not apparent and is beyond the scope of this study. The fetal heart may have difficulty recruiting any preload reserve because it probably functions at rest near the peak of the curve.

Although preload reserve is demonstrated by this study, we are unable to compare the relative degree of reserve of the fetal heart and mature hearts. It is difficult to develop volume controls to compare cardiac function in small immature and large mature-size hearts. Although such control methods have been suggested [24], they remain suspect.

This study confirms that preload reserve is present in the fetal heart. Judicious manipulation of the preload to affect cardiac output would seem appropriate in the management of fetuses and immature neonates.

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Surgical Management and Radiological Characteristics of Bronchogenic Cysts

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Forty-two patients with bronchogenic cysts were treated over a 30-year period (1962 to 1991). The location was mediastinal in 37 and intrapulmonary in 5. Cysts were symptomatic in 21 patients (50%) and complications occurred in 11 (26%). The complications included infection in 5 patients, hemorrhage into the cyst in 2 patients, dysphagia due to esophageal compression in 2, adenocarcinoma arising from a bronchogenic cyst in an 8½-year-old girl, and an esophagobronchopleurocutaneous fistula as a result of previous incomplete resection in 1 patient. Magnetic resonance imaging has been found to provide specific diagnostic information about broncho-

genic cysts. All but 2 patients were treated with complete excision. One patient was managed by observation and another had drainage of the cyst by mediastinoscopy. Complications of treatment occurred in only 2 patients. One had a minor wound infection and the other had *Clostridium difficile* enterocolitis. Only 4 patients were lost to follow-up. No late complication or recurrence developed in those patients having complete excision. We recommend complete excision in most instances to confirm the diagnosis, relieve symptoms, and prevent complications.

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Bronchogenic cysts are unusual congenital anomalies of lung development arising as a result of a group of cells that break off from the developing lung bud and differentiate on their own. They are usually found in the mediastinum around the tracheobronchial tree or in the pulmonary parenchyma. This apparently benign condition, however, can produce a variety of symptoms and complications. Bronchogenic cysts can present a diagnostic dilemma as well. The use of computed tomography, magnetic resonance imaging, and ultrasonography can differentiate these cystic lesions from other mediastinal tumors.

Material and Methods

Over a 30-year period (1962 to 1991), all patients with bronchogenic cysts managed at the Massachusetts General Hospital were reviewed. The medical records and radiographs of 42 patients were studied. Criteria for inclusion include histologically confirmed bronchogenic cysts ($n = 37$), mediastinal cysts of undetermined origin but strongly believed to be bronchogenic cysts because of the typical location and behavior ($n = 3$), and clinically diagnosed bronchogenic cysts with no specimen submitted for histological study ($n = 2$). Follow-up was obtained from patient contact or office records.

Results

Age and Sex

There were 16 male and 26 female patients with a male to female ratio of 1 to 1.63. The age range was 8 to 62 years with a mean age of 34.8 years.

Symptoms

Symptoms were present in 21 patients (50%). Pain was the most common symptom, and it occurred in 10 patients (24%). The pain was located substernally in 6 and over the lateral chest in 2. One patient had a ruptured infected cyst and presented with right upper quadrant abdominal pain associated with lateral chest and shoulder pain. Another patient had a cyst on the anterolateral aspect of the thoracic vertebral bodies and presented with pain between the scapulae. Other symptoms included cough in 7 patients (17%), fever in 4 (10%), dysphagia in 2 (5%), purulent sputum in 2 (5%), hemoptysis in 1 (2%), and mild shortness of breath in 1 (2%). Several patients had more than 1 symptom.

Location

There were 37 mediastinal and 5 intrapulmonary bronchogenic cysts. The location of the mediastinal bronchogenic cysts was classified according to Maier [1]. Carinal and paratracheal locations were the most common (9 each). Paraesophageal was the next most common (8 patients), followed by hilar (5 patients). There were 6 pathologically confirmed bronchogenic cysts located in unconventional locations: 2 in the anterosuperior mediastinum, of which 1 was actually inside the thymus gland; 1 intrapericardial;

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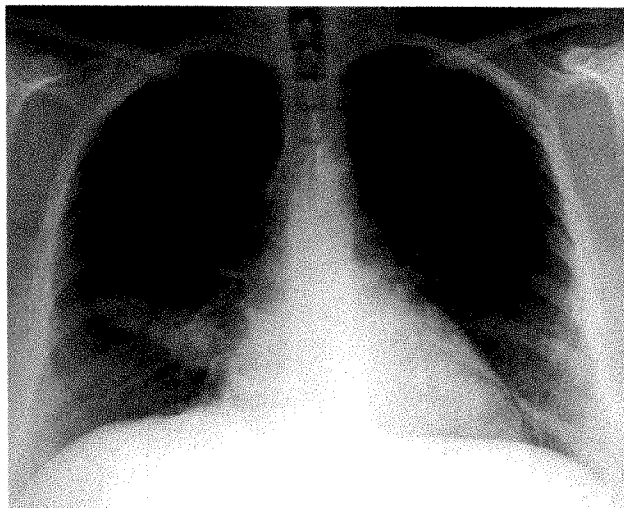


Fig 1. Bronchogenic cyst of the middle lobe showing homogeneous water density on a plain chest radiograph.

1 on the diaphragm; and 1 on the anterolateral surface of the thoracic vertebral bodies. One left hilar bronchogenic cyst was associated with a congenital defect of the adjacent pericardium. Our most recent patient had bilateral bronchogenic cysts as shown on chest radiograph, computed tomogram, and magnetic resonance imaging. The patient will undergo staged removal of the cysts, with the right-sided lesion having already been removed through a right thoracotomy. The lesions were thought to be inaccessible through median sternotomy. The intrapulmonary bronchogenic cysts did not show a predilection for any lobe. Two were in the right lower lobe and one each in the right middle, left upper, and left lower lobe.

Imaging

Standard chest radiographs identified the bronchogenic cysts in 37 patients (88%). The 5 not seen were all in the subcarinal position. Of those seen on standard radiographs, most presented as homogeneous water density shadows (Fig 1), whereas 2 patients had air-fluid levels (Fig 2). These 2 patients both had intrapulmonary lesions.

Barium swallow was performed in 14 patients and showed slight indentation of the esophageal image in 10 (71%).

Computed tomography was performed in 18 patients. The radiographic characteristics were those of a round, well circumscribed, unilocular or multilocular mass (Fig 3) with density ranging from water density (0 to 20 Hounsfield units [HU]) to as high as 91 HU. Occasionally computed tomography showed an air-filled cyst (Fig 4).

Magnetic resonance imaging was performed in 6 patients. In 1 of them, the cyst showed low signal intensity in T1-weighted images and bright signal intensity in T2-weighted images, indicating it was of low specific gravity and mainly serous. The other 5 cysts showed high signal intensity on both T1- and T2-weighted images (Figs 5, 6). This was due to the presence of a large amount of proteinaceous material or blood. The high signal intensity

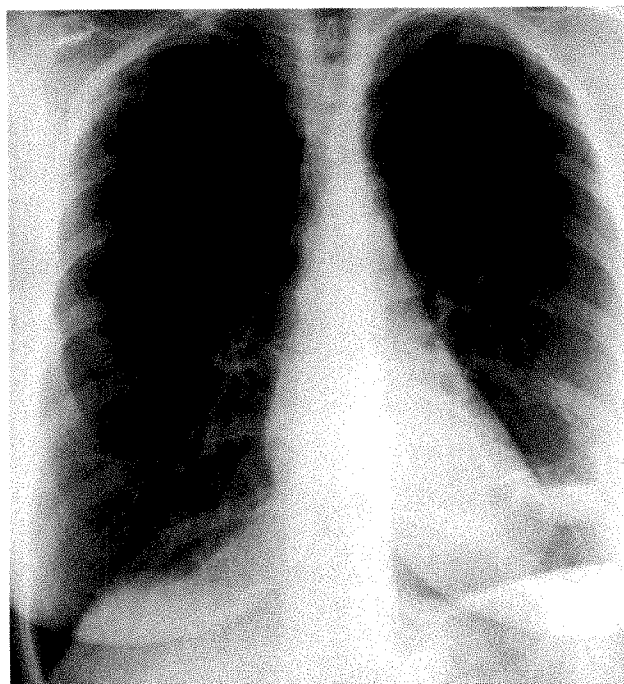


Fig 2. Bronchogenic cyst of the left lower lobe with bronchial communication. The cyst is air filled and shows an air-fluid level.

on T1-weighted images was not attributable to fat because this differentiation was made by comparison with a corresponding computed tomogram.

Ultrasonography was performed in 2 patients. The bronchogenic cyst in 1 was in the subcarinal location, whereas the other was in the retrocardiac paraesophageal region. In both patients, an anechoic lesion was found and confirmed the cystic nature of the mass.

Endoscopic Findings

Results of bronchoscopy were available in 26 patients. Abnormalities were found in 9 patients. Abnormalities

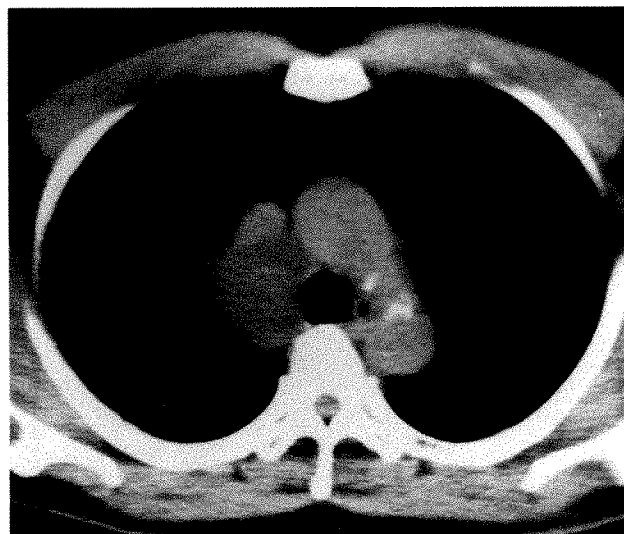


Fig 3. Unilocular homogeneous fluid-filled bronchogenic cyst at the right paratracheal region.

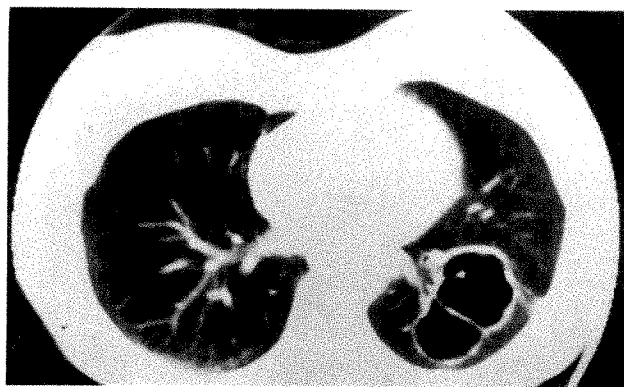


Fig 4. Multilocular air-filled bronchogenic cyst of the left lower lobe.

were predominantly related to extrinsic compression of the tracheobronchial tree by the bronchogenic cysts. Blood-tinged material was seen coming from the middle and lower lobes in 1 patient with infected cyst, and 1 patient had bronchoscopic evidence of direct communication to the bronchus intermedius from a cyst that had previously been incompletely excised.

Needle Aspiration Biopsy

Needle aspiration biopsy was performed in 2 patients. In 1 patient, a small amount of material with red blood cells and lymphocytes was found. There were also rare intracellular acid-fast-positive round bodies of uncertain significance. In the other patient, inflammatory cells, debris, mesothelial cells, histiocytes, and lymphocytes were



Fig 5. Coronal T1-weighted image showing a right prevertebral bronchogenic cyst with high signal intensity consistent with high protein content.

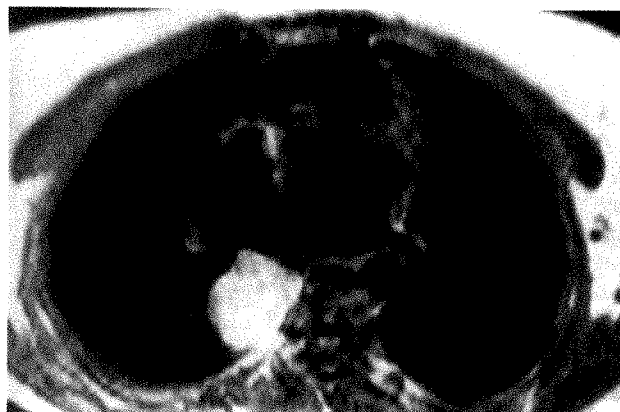


Fig 6. Axial T2-weighted image of the same bronchogenic cyst as in Figure 5 showing it exhibits bright signal intensity.

found. Needle biopsy was not thought to be helpful in establishing the diagnosis in these 2 patients.

Diagnosis

Preoperative diagnosis was accurately made in only 17 patients (41%). With the present new imaging techniques, accuracy was much higher in patients treated recently.

Complications

Complications of bronchogenic cysts occurred in 11 patients (26%). Esophageal compression resulting in dysphagia occurred in 2 patients. Dysphagia was transient in 1 but lasted for 1 year before resection in the other. Dysphagia in both was due to subcarinal bronchogenic cysts. Hemorrhage into the cyst occurred in 2 patients.

Bronchogenic cysts became infected in 5 patients. An infected paraesophageal bronchogenic cyst ruptured and caused pleuritis and partial collapse of the right lower lobe in 1 patient. Postobstructive pneumonia developed in 1 patient, and 2 patients with intrapulmonary bronchogenic cysts presented with purulent sputum. *Aspergillus fumigatus* was cultured from 1 of these patients. The fifth patient with infection was entirely asymptomatic. A left upper lobe intrapulmonary bronchogenic cyst was discovered on a routine chest radiograph. A left apicoposterior segmentectomy was performed to remove the cyst. Pathological examination showed a bronchogenic cyst with chronic inflammation of cyst lining with focal erosion and focal granulomas. Special stain did not reveal acid-fast bacilli or fungi, but a culture of a specimen of the cyst grew *Mycobacterium tuberculosis*. This patient received antituberculous treatment.

An 8½-year-old girl presented with a mass in the subcarinal region with near-total obstruction of the distal trachea and right main bronchus. A 2 × 3 × 3-cm mass adherent to the carina was removed, and the defect in the membranous portion of the carina was closed primarily. Pathological examination showed that the mass was an adenocarcinoma arising from a bronchogenic cyst. The patient was referred for carinal resection and reconstruction. A successful operation was performed, and pathological examination showed no residual cancer.

A 24-year-old patient presented with a fistula between a residual bronchogenic cyst and the bronchus intermedius. He had initially undergone an incomplete excision of a subcarinal bronchogenic cyst in another institution. One and a half years later, the patient presented with an esophagobronchopleurocutaneous fistula and mediastinitis. Several operations failed to correct the problem. The patient was referred to us and underwent successful resection of the residual cyst and closure of the bronchial fistula.

Treatment

Only 1 patient in our series was followed up without intervention because of multiple medical problems. The patient was asymptomatic and remained so for 12 years. One patient had evaluation of a large paratracheal mass with mediastinoscopy. A large fluid-filled cyst was entered, and 750 mL of brownish red fluid was removed. No further treatment was recommended because of other medical problems. The mass persisted in subsequent chest radiographs. Two patients underwent resection through a median sternotomy because a mediastinal tumor was suspected. The remaining patients underwent resection by either right ($n = 29$) or left ($n = 9$) thoracotomy. The patient who has bilateral bronchogenic cysts will undergo left thoracotomy to complete the removal of the left-sided component at a later date. In all but 3 mediastinal bronchogenic cysts, only the cyst itself was removed. The thymus gland was removed as well in 1 patient because the bronchogenic cyst was in the thymus gland. An ellipse of pericardium was removed in 2 patients because of adherence. In the patient who had a ruptured infected paraesophageal bronchogenic cyst, decortication and drainage of the empyema was performed. In 4 patients, the bronchogenic cysts were so adherent to the tracheobronchial tree that either the trachea or the main bronchi were entered during dissection, creating a small defect in the membranous wall. The defects in the airway were closed successfully without further complications. In all intrapulmonary cysts, pulmonary resection was required. Wedge excision ($n = 1$), segmentectomy ($n = 1$), and lobectomy ($n = 3$) were performed to enable complete removal of the bronchogenic cysts.

Morbidity and Mortality

Postoperative complications occurred in only 2 patients. A minor wound infection developed in 1 patient, and *Clostridium difficile* enterocolitis secondary to perioperative antibiotics developed in another. There was no operative mortality. Median hospital stay was 7.9 days (range, 2 to 23 days).

Pathological Findings

Specimens were available for pathological examination in 40 of the 42 patients reported. Typical histological features included a ciliated columnar epithelial lining and a connective tissue wall with or without cartilage in 37. Three of the specimens were cysts that did not show recognizable epithelium but were believed strongly by us to be bron-

chogenic cysts because of their typical location and behavior. The size of the bronchogenic cysts ranged from 2 to 12 cm in the maximum diameter, with an average of 5.3 cm. Noniatrogenic bronchial communication was found in 3 patients. Two of them had intrapulmonary cysts that showed a fluid level on standard radiographs, and the third had a subcarinal cyst with two tiny communications with the left main bronchus discovered during operation. Cysts were unilocular in 29 patients, multilocular in 7, and aggregates of cysts in 4. Evidence of either acute, chronic, or granulomatous inflammation was found in 7 patients. The content of the cysts showed a great variety of color and consistency.

Follow-up

Only 4 patients were lost to follow-up. Thirty-four patients were contacted personally, and follow-up information was obtained from the office records of 4 patients. There were no late complications and no instance of recurrence of the cyst. The follow-up period ranged from 1 month to 26 years (mean, 8.2 years).

Comment

The first report of a bronchogenic cyst was in 1859 by Meyer [2]. By 1952, only about 100 cases were reported in the literature. Since then, numerous reports have appeared. Bronchogenic cysts account for about 5% to 10% of mediastinal masses.

Bronchogenic cysts can be found in a great variety of locations. Most bronchogenic cysts originate in the mediastinum with a smaller percentage occurring in the lung parenchyma, as in our series. They can occur in many atypical locations ranging from the neck [3, 4] to intradural [5] to below the diaphragm [6, 7].

Although many bronchogenic cysts are benign and asymptomatic and represent incidental findings on radiograph, many complications including lethal ones have been reported. Infection is a common complication, especially in those cysts with bronchial communication. Tracheobronchial compression can occur in children because of the relatively soft tracheobronchial tree [8]. Pressure on the adjacent esophagus can result in dysphagia. Superior vena caval obstruction has been reported by several authors [9, 10]. Pressure on the heart can produce arrhythmia [11] or obstruction of the right ventricular infundibulum, main pulmonary artery [12], right pulmonary artery [13], or left pulmonary artery [14]. The cyst can rupture into the trachea [15], the pericardial cavity [16], or the pleural cavity as in 1 of our patients. Malignancy has been associated with bronchogenic cysts. The first report was by Moersch and Clagett [17] in 1947, in which they reported one adenocarcinoma in 36 bronchogenic cysts and one squamous cell carcinoma found in a ciliated cyst of indeterminate origin. In 1951 Behrend and Kravitz [18] described a sarcoma arising from a bronchogenic cyst. Prichard and associates [19] reported two adenocarcinomas from large peripheral lung cysts, one thought to be bronchogenic in origin.

The radiographic characteristics of bronchogenic cysts

have been well defined by others [20]. Intrapulmonary bronchogenic cysts are usually sharply defined, solitary, noncalcified, round or oval opacities confined to a single lobe, usually a lower lobe. The cysts change little in size over a long period of time. They can present as a homogeneous water density, as an air-filled cyst, or with an air-fluid level. The wall is usually very thin, measuring 1 to 2 mm, and fine septa may be seen crossing through the cyst. Mediastinal bronchogenic cysts are usually homogeneous, smooth, solitary, round or ovoid, noncalcified masses located in the middle, posterior, or superior mediastinum in close association with the trachea or major bronchi.

Computed tomography has proven to be helpful in the diagnosis of bronchogenic cysts and often demonstrates a cyst not visible by conventional radiographic techniques. Computed tomography is also very useful in demonstrating the relation of bronchogenic cysts to other mediastinal structures. The computed tomographic density of bronchogenic cysts can vary from typical water density (0 to 20 HU) to high density (89 to 99 HU), as illustrated in 1 of our patients. Higher computed tomographic numbers represent increased calcium content, anthracotic pigment, blood, or greater protein content of the fluid [21]. Computed tomographic density up to 130 HU has been reported in adult patients [22].

Magnetic resonance imaging may provide specific diagnostic confirmation in regard to bronchogenic cysts. The magnetic resonance appearance is dependent on the cyst's content, specifically the presence and amount of mucus or other proteinaceous material. If the fluid within a bronchogenic cyst is of low specific gravity and mainly serous (a spring water cyst), it will be of very low signal intensity on T1-weighted images and of very bright signal intensity on T2-weighted images. However, many bronchogenic cysts may contain large amounts of proteinaceous material. Such cysts have a characteristic appearance with high signal intensity on T1-weighted images. This appearance must be differentiated from lesions that contain fat, which also has bright signal intensity on T1. However, that differentiation can easily be made by comparison with a corresponding computed tomogram. Fatty lesions will be of low attenuation on computed tomograms. Such bronchogenic cysts will have slightly diminished signal intensity on T2-weighted images, and they will often display either fluid/fluid levels or areas of heterogeneity. We believe that magnetic resonance imaging can diagnose bronchogenic cysts accurately and is indicated to confirm the diagnosis, especially when the surgeon does not want to operate on the patient. When the cyst is in a suitable location, ultrasound can be a useful tool to demonstrate the cystic nature of the lesion, as was done in 2 of our patients.

Percutaneous needle aspiration can be used for diagnostic purposes or even therapeutic purposes if thin fluid is present within the cyst. This technique for diagnosis was used only twice in our series and was not helpful in either case. Simple aspiration as a form of treatment is likely to have a high recurrence rate because the lining of the cyst is not obliterated.

Mediastinoscopy has been used to evaluate and treat bronchogenic cysts. Some authors have advocated removal of the cysts piecemeal with biopsy forceps through the mediastinoscope [23]. If the cyst wall remains intact, a high recurrence rate can be expected. Caution should be exercised in using this method for infected cysts.

We advocate complete excision in most cases. Often the diagnosis is in doubt and malignancy is suspected. Little doubt exists about the need to excise symptomatic cysts. We prefer to excise known asymptomatic bronchogenic cysts because of the risk of complications. The high rate of complications that we observed confirms the recent observations of St-Georges and associates [24]. In certain patients, observation is acceptable if the diagnosis is established and the patient is asymptomatic. Development of symptoms or a change in size warrants excision. If excision is undertaken, complete excision should be the goal. Incomplete excision will lead to a high recurrence rate and the potential for more serious complications as in our patient in whom an esophagobronchopleurocutaneous fistula developed. Any communication with the tracheobronchial tree should be carefully closed and buttressed with local, healthy tissue whenever possible. Intrapulmonary bronchogenic cysts should be excised because of the high incidence of secondary infection associated with them. Lung-sparing procedures compatible with complete excision should be done because of the benign nature of most of these cysts.

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De Vega's Semicircular Annuloplasty for Tricuspid Valve Regurgitation

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Moderate to severe functional tricuspid regurgitation was found in 26% of cardiac surgical patients with mitral or aortic valvular disease at Tri-Service General Hospital in Taiwan. Almost all patients were able to receive de Vega's annuloplasties. After a mean follow-up period of 20 months, none of the 63 patients had moderate or severe tricuspid regurgitation. There was no heart block or right atrial thrombosis; the single late death was not

related to the heart disease. De Vega's tricuspid annuloplasty is considered to be a safe, effective, and durable procedure in the treatment of functional tricuspid regurgitation. Compared with tricuspid valve replacement and other types of annuloplasty, the de Vega is the first choice here.

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Tricuspid regurgitation (TR) may be present in 10% to 50% of patients with severe mitral stenosis or regurgitation [1, 2]. In a majority of patients, this condition is functional in nature, secondary to pulmonary hypertension and right ventricular dilatation [3, 4]. Spontaneous regression of functional TR after repair of the mitral lesion is in some cases impossible, and tricuspid valve annuloplasty (TVA) or even tricuspid valve replacement (TVR) is inevitable [1]. Tricuspid valve annuloplasty is a simple, safe, effective, and reliable surgical procedure for which there are several techniques. Although some surgeons prefer to do TVA with a Carpentier ring [5], the semicircular annuloplasty introduced by de Vega [6] is one of the simplest and easiest methods. Here, experience and mid-term results in this hospital, using de Vega's TVA in patients with functional TR, are described.

Material and Methods

Patients

Between January 1987 and May 1991, mitral or combined mitral and aortic valve operations were carried out in 176 patients, and de Vega's TVA was performed in 63 patients. Of the patients having de Vega's TVA, 43 were female and 20 were male, with an average age of 48.2 ± 12.9 (standard deviation) years (range, 12 to 74 years).

Preoperative diagnosis of TR was made by echocardiograms and was confirmed by finger palpation intraoperatively. Doppler echocardiography was performed before, and bimonthly after, operation to determine the severity of TR graded by the percent area of the regurgitant flow of the right atrium as follows: grade 1 = minimal flow, grade 2 = less than 20%, grade 3 = 20% to 40%, and grade 4 = more than 40%.

Indications for TVA were (1) TR of grade 3/4 or more as determined by right ventriculography, (2) TR of grade 3 or more as evaluated by Doppler echocardiography, or (3) moderate to severe TR as assessed by digital palpation through the right atrial appendage before the institution of cardiopulmonary bypass.

Concomitant procedures carried out at the time of tricuspid valve operation were mitral valve replacement in 34 patients, combined aortic and mitral valve replacement in 11 patients, aortic valve replacement in 1 patient, mitral valve commissurotomy in 2 patients, closure of atrial septal defect in 10 patients (including 1 patient with Holt-Oram's syndrome), and pulmonary valvotomy in 1 patient. Only 4 patients had simple TVA without other concomitant procedures.

The TR in all patients who underwent TVA was functional. Causes were mitral or aortic valve disease in 49 patients, atrial septal and pulmonary hypertension in 9 patients, pulmonary valve stenosis in 1 patient, arrhythmia-induced right ventricular dysplasia in 1 patient, hyperthyroidism in 1 patient, Holt-Oram's syndrome in 1 patient, and unknown in 1 patient.

Tricuspid valve replacement was performed in 22 patients during the same study period. Among these patients, 16 (73%) had organic change of the tricuspid valve: previous tricuspid valve replacement in 2 patients, subacute bacterial endocarditis of the tricuspid valve in 5 patients, Ebstein's anomaly in 1 patient, rheumatic tricuspid valve stenosis in 5 patients, and traumatic tricuspid valve regurgitation in 3 patients. Only 6 patients (27%) had functional TR: failed de Vega's annuloplasty in 4 patients, recurrent TR after annuloplasty in 1 patient, and TR caused by atrial septal defect and severe pulmonary hypertension in 1 patient.

Operative Technique

Under general anesthesia, a median sternotomy was done. The aorta, superior vena cava, and inferior vena

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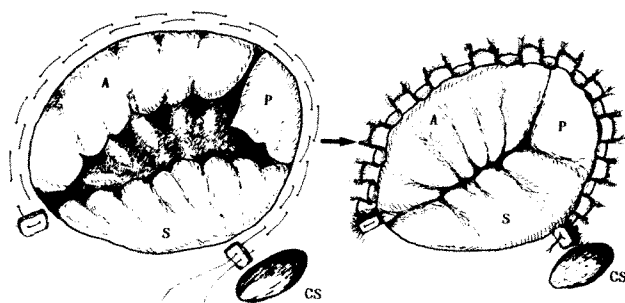


Fig 1. Suture techniques of de Vega's tricuspid valve annuloplasty: Two semicircular pursestring sutures, made with the same 2-0 polypropylene stitch, are started from the anteroseptal commissure and penetrate the annulus until the midportion of the coronary sinus. The two rows of sutures are parallel, but the sequences of penetration are alternative so that homogeneous narrowing of the annulus is achieved. (A = anterior leaflet; CS = coronary sinus; P = posterior leaflet; S = septal leaflet.)

cava were cannulated, and the patients were put on cardiopulmonary bypass. Moderate hypothermia and hemodilution techniques were employed. Before cardiopulmonary bypass, an average of 500 mL of autologous blood was collected for postoperative transfusion. The aorta was cross-clamped, and crystalloid cardioplegic solution was infused into the aortic root. Left-sided heart lesions were corrected first; then the right atrium was opened and the tricuspid valve was thoroughly examined. If there were no structural change on the leaflets, then TVA would be performed. A 2-0 polypropylene suture with Teflon felt was placed in the annulus, beginning at the commissure between the anterior and septal leaflets. The suture was continued along the tricuspid annulus, and ended at the coronary sinus to form a pursestring. The other arm of the suture was used to make a similar pursestring, but in an alternative sequence to bring the stitches in and out of the annulus (Fig 1). Penetration depth of the stitches was 3 to 5 mm. Sutures were then tied to narrow the tricuspid annulus. A 31-mm valve sizer was placed in the annulus during suture tying to achieve a proper size annulus. Two silver clips prevented the knots from loosening.

After TVA, cold saline solution was rapidly flushed into the right ventricle to test the competency of the tricuspid valve. If the tricuspid valve and the right ventricle could be distended with solution and without substantial leakage, the right atrium was closed. Substantial leakage of solution from the tricuspid valve was an indication to do a valvular replacement.

Follow-up

Patients were followed up, as outpatients, by Doppler echocardiography every 2 months. The mean follow-up period was 20.0 months with a range of 3 to 41 months.

Results

Incidence

The incidence of functional TR in patients who received mitral or combined mitral and aortic valve operations is 46 of 176 or 26%.

Immediate Successful Rate

Of the 67 patients who received de Vega's TVA, only 4 had serious leakage from the tricuspid valve during intraoperative saline flushing test; these finally received TVR. The other 63 patients performed well and had no serious TR detected by finger palpation after being taken off the cardiopulmonary bypass. Thus, the immediate rate of success of TVA during the operation was 94%. There was no operative mortality.

Follow-up Study

The preoperative severity of TR as assessed by Doppler echocardiography was grade 3 in 18 patients (29%) and grade 4 in 45 patients (71%). After a mean follow-up period of 20 months postoperatively, 17 patients (27%) had no TR, 42 patients (67%) had grade 1 TR, and 4 patients (6%) had grade 2 TR; no patient had grade 3 or grade 4 TR. Of those patients with grade 2 TR after the operation, none had residual left-sided heart lesion; their daily demand for diuretics was 20 to 40 mg of furosemide, and was not higher than that of other patients. Only 1 patient, whose TR was caused by arrhythmogenic right ventricular dysplasia, had persistent right heart failure after the operation. As to the functional status, 29 patients (46%) were in New York Heart Association functional class I, 31 (49%) were in functional class II, and 3 (5%) were in functional class III.

Mortality

There was no hospital mortality. One patient died of intracranial hemorrhage 2 months after the operation, possibly from a coumarin overdose. There has been no late death.

Complications

One patient had postoperative bleeding and was reopened for bleeding check. Another patient was reoperated on for paravalvular leakage from the prosthetic mitral valve. Two further patients suffered stroke during hospitalization. There was no conduction disorder either early or late after the operation.

Reoperation

No patient has had development of recurrent TR severe enough for reoperation during this study period.

Comment

Tricuspid regurgitation may be functional or organic. Functional TR is commonly secondary to left heart lesions, which lead to dilatation of the right ventricle and the tricuspid annulus; organic TR may be secondary to rheumatic fever, trauma, carcinoid syndrome, or subacute bacterial endocarditis. Although Braunwald, Ross, and Morrow [7] reported that secondary tricuspid regurgitation generally resolves after a successful mitral valve operation, other authors report different experiences [2]. Goldman and associates [8] reported that residual TR after mitral valve operations may significantly increase postoperative morbidity and mortality, and suggested detection

of TR by routine echocardiography. Boyd, Reed, and their colleagues [9, 10] reported that 22% to 30% of patients with mitral valve disease have associated TR. In this series, of the 176 patients who underwent mitral or combined mitral and aortic valve operations, 46 patients (26%) had concomitant moderate to severe TR. Thus the incidence here was similar to that in other series.

Of 48 patients who had left heart valvular diseases, 47 had either mitral or combined mitral and aortic valve lesions; only 1 patient had a single aortic valve lesion. This condition indicates that mitral valve lesion causes pulmonary hypertension and subsequent right ventricular dilatation and TR, whereas aortic valve lesion causes dilatation of the left ventricle and is less likely to cause TR.

The tricuspid valve is the largest valve in the heart, with an average area of 10.5 cm² and an average diameter of 36 ± 4.5 mm [11]. It has three leaflets: anterior (the largest), posterior, and septal. The anterior leaflet commonly attaches to a single major papillary muscle, whereas the posterior and septal leaflets generally directly attach to the right ventricular wall with chordae tendineae [11]. The conduction system penetrates the base of the septal leaflet; thus, this part of the annulus should not be sutured during annuloplasty. With right ventricular dilatation, the tricuspid annulus enlarges along the major portion of the attachment of the anterior leaflet, the posterior leaflet, and the lateral third of the septal leaflet. For this reason most annuloplasties shorten the annulus at the anterior and posterior leaflets [5].

The degree of functional TR is related to the following factors: (1) the severity of left-sided lesion, (2) the duration of the left-sided lesion, (3) the severity of pulmonary vascular resistance and pulmonary hypertension, and (4) the degree of right ventricular dilatation [11].

The optimal goal of the treatment of valvular insufficiency is reconstruction instead of replacement. Not all cases of mitral insufficiency, and few cases of aortic insufficiency, can be repaired. Functional tricuspid insufficiency, however, can be repaired in almost all cases. In this series, TVA was unsuccessful in only 4 of 67 patients.

All the complications related to valve prostheses may occur in TVR. Thrombosis of the mechanical prosthetic valve in the tricuspid position has varied between 4% and 30% [12-14]. Although bioprostheses have lower thrombogenicity in the tricuspid position, calcification and degeneration remain the chief problems [15, 16]. Another problem with TVR is the inequity between the prosthesis and the right ventricular cavity. The particular configuration of the right ventricle has been thought to be detrimental to the ideal functioning of a valve prosthesis. Complete heart block occasionally develops late after TVR, especially when a combined mitral valve replacement is performed. This association is undoubtedly related to the interposition of the atrioventricular node between the two replacement devices. Kirklin [17] reported that about 10% of patients receiving both tricuspid and mitral replacement require insertion of a pacemaker postoperatively because of heart block; up to 10 years postoperatively, the actuarial incidence is 25%. Present results show no heart block and thrombosis in patients

who received TVA. For these reasons, TVA is preferable to TVR in the treatment of functional TR.

However, TVA is unsuitable for organic TR. In organic TR, the tricuspid valve is destroyed and has to be replaced because deformed tricuspid valve leaflets cannot be corrected by simply narrowing the annulus.

In this series, 10 patients with atrial septal defect (including 1 patient with Holt-Oram's syndrome) had development of TR and needed TVA. The mechanism of TR might be the same as functional TR caused by mitral valve disease, ie, the dilatation of the right ventricle. Most of these patients were adults with pulmonary hypertension, which might have been responsible for right ventricular dilatation.

Two other methods of annuloplasty are commonly used for TVA: (1) Kay or Wooler [9] TVA, which is bicuspidalization of the tricuspid valve by making sutures to obliterate most of the posterior annulus, and (2) Carpentier [5] TVA, in which interrupted sutures are made from the tricuspid valve annulus to a ring with a C-shaped configuration open at the area of the penetrating bundle of His. Grondin and associates [18] reported that the Carpentier's and de Vega's annuloplasties appear superior to Kay's bicuspidalization annuloplasty according to hemodynamic studies after 11 and 10 months. In contrast, Péterffy and colleagues [19] and Nakano and associates [20] reported that Kay's and de Vega's annuloplasties gave similar and good late results in about 70% of the patients. At this hospital, no comparison has been made of results of de Vega's annuloplasty with those from other techniques, but the data show that de Vega's annuloplasty resulted in nearly total satisfaction after a mean follow-up period of 20 months. In these 63 consecutive patients, the actuarial survival rate was 98.4%, and the actuarial rate of freedom from reoperation on the tricuspid valve was 0%. Almost no patient (93.7%) had even minimal TR during the follow-up, and no patient had grade 3 or more TR after operation. This early experience with de Vega's annuloplasty has shown that the sutures should be deep enough to hold the annular tissue strongly to avoid cutting through the tissue after the heart resumes the contraction. Another factor that might be related to good outcome in our patients is that narrowing of the TV annulus is more homogenous when the pursestring sutures are made in an alternative sequence.

We conclude that (1) de Vega's TVA is an effective, reliable, and durable technique in treatment of functional TR; (2) de Vega's TVA can be performed in almost all patients with functional TR; (3) de Vega's TVA seldom causes the heart block and thrombosis that commonly occur in TVR; (4) de Vega's TVA saves heart ischemic time and reduces operative risk; (5) de Vega's TVA needs no prostheses and is the least expensive way to treat functional TR; and (6) de Vega's TVA is the treatment of choice for functional TR.

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INVITED COMMENTARY

This is a summary of results in 63 patients with moderate or severe tricuspid regurgitation that resulted from "functional" tricuspid annular dilatation, secondary to left-sided valvular heart disease. Interestingly, this was the most common cause in this series from the Republic of China, yet this is also the most common cause of tricuspid valve regurgitation in North America. Wei and associates stress that for this diagnosis the necessity of replacing the tricuspid valve is virtually nil with current day techniques, a concept I totally endorse. They have used the de Vega semicircular annuloplasty, whereas we have adopted a variation of this technique using only a posterior de Vega-type annuloplasty. Pathophysiologic studies from a number of centers have indicated that the primary site of the dilatation of tricuspid annulus is the posterior aspect, which is more or less the free margin of the tricuspid valve. Thus, an annuloplasty beginning at approximately 12 o'clock and extending to approximately 6 o'clock, tied down over an obturator in the valve orifice, will suffice for almost all patients with moderate tricuspid regurgitation.

For severe tricuspid regurgitation, however, I take a different tack than Wei and associates, and advise tricuspid ring annuloplasty. I think that the high recurrence rate of the de Vega-type extensive semicircular annulo-

plasty previously recorded has been in the massively dilated tricuspid annulus with severe signs of right-sided congestive failure, including hepatomegaly and ascites. In this clinical syndrome, the annular tension on the annuloplasty stitch may be enormous, and a high incidence of recurrence has been reported in massive tricuspid regurgitation. Here the rigid Carpentier ring or the flexible Duran ring gives more solidity to the repair and is strongly advised for the patient with massive tricuspid regurgitation. Wei and associates have done an excellent job in presenting the case for repair of the tricuspid regurgitation. With the standardization of tricuspid annuloplasty techniques, it is clear that this defect can be ameliorated in the vast majority of patients by reconstructive techniques using both the semicircular or other suture techniques as well as ring annuloplasty techniques in patients with severe hemodynamic compromise by tricuspid regurgitation.

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Reoperative Coronary Artery Bypass Grafting Without Cardiopulmonary Bypass

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Between June 1979 and January 1992, 46 men and 13 women aged 35 to 81 years (mean, 58 years) underwent reoperative coronary artery bypass grafting without cardiopulmonary bypass. Isolated reoperative circumflex bypass was performed through a left thoracotomy, and reoperative bypass to the right coronary artery and left anterior descending coronary systems was through a median sternotomy. Complete revascularization was the goal in all patients. Saphenous vein grafts were placed to the right coronary artery (n = 21), circumflex artery (n = 11), and left anterior descending artery (n = 24), and 14 internal thoracic artery to left anterior descending artery bypass grafts were performed. The overall mortality rate was 3.4% (2 deaths). Postoperative morbidity included

myocardial infarction in 1 patient and pleuropulmonary complications in 6. No patient was reexplored for hemorrhage, and 19 patients required no blood products. Twenty patients underwent repeat coronary angiography, and 18 of 20 grafts placed without cardiopulmonary bypass were patent. At a mean follow-up interval of 42.2 months 35 of 50 evaluable patients were in functional class I or II. In selected patients, reoperative coronary artery bypass grafting can be performed without cardiopulmonary bypass with a low perioperative morbidity and mortality rate, satisfactory graft patency rates, and good long-term symptomatic improvement.

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A recent survey of open heart surgery in New York State demonstrated that almost 10% of all adult cardiac surgical procedures were reoperations, with the majority being myocardial revascularization [1]. As the overall experience with reoperative coronary artery bypass grafting (CABG) has increased, alternative strategies have evolved in an attempt to lower the operative risks, which exceed those of initial revascularization [2]. These include different techniques for sternal reentry, strict avoidance of graft manipulation to minimize the risk of graft atheroembolism, and modifications in the method of

For editorial comment, see page 329.

myocardial protection depending on the status of the native coronary circulation and patency of vein or internal thoracic artery (ITA) grafts. As an alternative method of "myocardial protection" and to obviate the inherent risks of cardiopulmonary bypass, we have performed reoperative CABG without cardiopulmonary bypass (CPB) in a carefully selected group of patients. This report outlines that experience.

Material and Methods

Patients

From June 1979 to January 1992, 59 patients underwent reoperative CABG without CPB. Over the same time frame 540 patients underwent reoperative CABG with

CPB. Elective operations were performed in 44 patients with chronic angina refractory to medical therapy. Nineteen patients in this group had previously undergone one to six prior coronary angioplasty procedures. Eleven patients were operated on urgently because of unstable angina requiring intravenous nitroglycerin and heparin, and 4 patients were surgical emergencies because of coronary occlusion after a failed coronary angioplasty.

The group of patients consisted of 46 men and 13 women aged 35 to 81 years (mean age, 58 years). Twelve patients were older than 70 years, including 2 patients aged 81 years. Eleven patients had suffered a prior myocardial infarction. Left ventricular ejection fraction in this group ranged from 0.16 to 0.75 (mean, 0.48). Fifty-six patients underwent their first and 3 their second reoperation for myocardial revascularization.

This technique was used in two situations: (1) Patients in whom target vessels were limited to the right coronary artery (RCA) and left anterior descending (LAD) coronary systems with either an undiseased or nongraftable circumflex (Cx) system or patent and nondiseased Cx grafts (n = 48) were reoperated on through a median sternotomy. (2) Patients in whom target vessels were limited to the circumflex system and the RCA and LAD grafts were angiographically normal (n = 11) were operated on through a left thoracotomy. Complete myocardial revascularization was the goal in all patients. Vein grafts were not routinely replaced if they were angiographically normal.

Forty-eight patients underwent single-vessel CABG including single aortocoronary vein grafts to the RCA (n = 15), LAD (n = 12), and Cx (n = 11) and 10 left ITA to LAD

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bypass grafts. Eleven patients underwent two-vessel bypass with distal vein graft anastomoses performed to the RCA ($n = 6$), LAD ($n = 7$), and left anterior diagonal ($n = 5$), three left ITA to LAD bypass grafts, and 1 right ITA to LAD bypass graft.

Technique

All patients were monitored with radial arterial, central venous, and pulmonary arterial catheters. In the 48 patients reoperated on through a median sternotomy, standard techniques were employed for sternal reentry. The heart and ascending aorta were dissected free of adhesions to the extent required for satisfactory exposure. When appropriate, a second surgical team harvested an appropriate length of saphenous vein. When the ITA was to be used, it was prepared after the lysis of adhesions. The patient was systemically heparinized with 100 U/kg of sodium heparin, and the proximal saphenous vein to aortic anastomosis was constructed with running 5 or 6-0 Prolene (Ethicon, Somerville, NJ) using partial aortic occlusion. The graft flow was assessed and its length tailored appropriately.

When the RCA was grafted, the acute margin of the heart was retracted with a stay suture placed in the epicardium. The distal RCA was dissected free at the chosen site of anastomosis and surrounded with fine silk traction sutures. A 7-mm longitudinal arteriotomy was made, and one or two stay sutures of 7-0 Prolene were placed at the midportion of the arteriotomy to facilitate exposure of the lumen of the RCA. The distal saphenous vein to RCA anastomosis was then made with running 6-0 or 7-0 Prolene. The graft was deaired and flow reestablished. The technical details for LAD or diagonal grafting were similar. Exposure was obtained by elevating the heart on a laparotomy pad, and the hemodynamic response was observed. Mild hypotension was easily corrected with volume or pressor administration, usually phenylephrine hydrochloride (Neosynephrine; Winthrop Consumer Products, New York, NY). Occasionally, use of the ITA retractor to elevate and laterally distract the left side of the chest proved beneficial.

Reoperative coronary artery bypass to the circumflex system was performed through a standard left anterolateral or posterolateral thoracotomy using a double-lumen endotracheal tube. The left lung was collapsed and the pericardium was opened anterior to the phrenic nerve. The proximal anastomosis was performed to the left subclavian artery, and the distal anastomosis to the appropriate Cx marginal branch was constructed using the technique described above. Interrupted sutures were occasionally employed at the toe of the distal anastomosis, especially if the artery was less than 2 mm in diameter. Standard closure of the median sternotomy or thoracotomy wound was employed using one or two chest tubes. Temporary pacing wires were employed as required. In general the decision to perform CABG without CPB was made based on the intraoperative inspection of the coronary artery size and location as well as the hemodynamic response to cardiac distraction.

Results

In this consecutive series there were two postoperative deaths (3.4%). The first was in a 73-year-old woman with known cerebrovascular disease and two prior strokes who underwent two-vessel bypass grafting to the LAD and diagonal coronary arteries. Her postoperative course was unremarkable until she suffered an extensive hemispheric stroke on the third postoperative day, which proved fatal. The second death occurred in a 71-year-old man with angina at rest requiring intravenous heparin and nitroglycerin that could not be weaned. His left ventricular ejection fraction was less than 0.20, with a left ventricular end-diastolic pressure in excess of 30 mm Hg. His native coronary circulation was occluded, and the only patent vein graft (to the LAD) had extensive graft atherosclerosis. This patient was referred for reoperation as a "salvage" procedure, and based on prior experience, it was thought that this technique was applicable. Intractable cardiac failure developed after sternotomy, and he was noted to have free-floating atheroembolic debris when the LAD was opened. Despite regrafting of the LAD and RCA, inotropic support, and intraaortic balloon pump support, he died of low cardiac output syndrome in the operating room caused by presumed vein graft atheroembolism. Possibly, this patient's outcome may have been different with more traditional methods of revascularization; however, because of his very poor ventricular function and the strong clinical suspicion of coronary atheroembolism, the situation was thought to be irretrievable and he was not placed on CPB. We fully recognize the potential criticism of this patient's management; however, in our experience there were no other patients in whom an attempt at CABG without CBP resulted in hemodynamic or rhythm disturbance requiring CPB to complete the procedure. No other patient in this series required intraaortic balloon pump support. Five patients required inotropic support in the postoperative period for a cardiac index less than $2 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$, and these 5 patients were weaned off all inotropes in the first 24 postoperative hours. No patient required ventilatory support longer than 48 hours.

Pleural effusions requiring tube thoracostomy or thoracentesis occurred in 5 patients. One patient had a prolonged air leak for 10 days after emergent single-vessel bypass grafting to the Cx marginal through a left thoracotomy after a failed percutaneous transluminal coronary angioplasty. An acute inferior myocardial infarction occurred in a 52-year-old man 1 day after left ITA to LAD bypass grafting. This patient's RCA and Cx grafts were occluded, as was the native circulation, and neither was thought to be graftable. He made an uneventful recovery.

No patient required reoperation for hemorrhage. Nineteen patients required no blood products. The average blood requirement in the remaining 40 patients was 1.2 units per patient. The majority of operations were performed when the indications for blood transfusion were more liberal, and only 5 of the last 17 patients required blood postoperatively. There were no wound infections. Of the 57 survivors, 39 were discharged on or before the

seventh postoperative day and 18 between postoperative days 8 and 17.

Twenty patients underwent repeat left heart catheterization and coronary arteriography at intervals varying between 2 weeks and 108 months postoperatively (mean, 24 months) because of recurrent chest pain syndromes. Eighteen of 20 grafts placed without CPB bypass were patent, including all vein grafts to the diagonal (1), RCA (9), and LAD (4). Three of four left ITA to LAD grafts and one of two Cx grafts restudied were patent. The cause of the recurrent chest pain in the 2 patients with graft occlusion was obvious. In 2 additional patients there was new vein graft atherosclerosis in grafts that were angiographically normal and 4 and 6 years old at the time of CABG without CPB; this was presumably the cause of recurrent chest pain. The cause of the chest pain in the remaining 16 patients was never clearly defined, but resolved without specific therapy.

The 57 survivors were seen at 1-month follow-up and were clinically improved. Seven of 57 survivors were lost to long-term follow-up. In the remaining 50 patients, follow-up ranged from 1 month to 11 years (mean, 42.2 months). Thirty-five were in New York Heart Association functional class I or II. Four patients were in functional class III to IV, 3 with chronic congestive heart failure and 1 with disabling angina. Three patients underwent a second coronary reoperation, 1 because of occlusion of a left ITA to LAD graft placed without CPB and 2 because of vein graft atherosclerosis. Eight patients died during the follow-up interval, 4 of presumed cardiac causes.

Comment

Coronary artery bypass grafting was first conceived and performed on dogs by Alexis Carrel in 1910 [3]. Murray and associates [4] "rediscovered" the operation in 1954 but did not recognize Carrel's contributions. In 1962 Sabiston [5] performed the first aortocoronary bypass graft in a human using saphenous vein, and in 1966 Kolesov [6] reported left ITA to LAD bypass grafting. These early attempts at direct surgical coronary revascularization were all performed on a beating heart without CPB. In 1970, Favaloro and colleagues [7] presented the Cleveland Clinic's initial experience with CABG and fueled the precipitous increase in direct coronary artery surgery in this country. In their report they recommended full CPB for revascularization of the left coronary artery but observed that in most patients bypass of the RCA could be done safely without circulatory support. Although virtually every facet of the operation has undergone numerous technical modifications, ranging from the method of myocardial protection to the type of conduit used, the vast majority are performed with total CPB. Although perfusion techniques continue to improve, there is still the potential for substantial morbidity and mortality associated with CPB, especially with the prolonged pump runs often required with reoperative procedures. To obviate the hazards of CPB, several groups have reported CABG without CPB.

In 1975, Trapp and Bisarya [8] reported 63 patients in

whom CABG was performed without CPB. Their technique involved a cumbersome, but seemingly effective system of coronary artery perfusion proximal and distal to the anastomotic site. Their report included no short-term or long-term follow-up data. In the accompanying editorial, Ankeney [9] expressed cautious support based on a personal experience with the technique, although he stated the coronary perfusion technique of Trapp and Bisarya was unnecessary. He emphasized the need to document graft patency and the incidence of perioperative myocardial infarction using this technique before it could be considered comparable with surgical revascularization using CPB. Strangely, Ankeney never published his results.

Faro and associates [10] demonstrated the feasibility of reoperative revascularization of the Cx or LAD systems in 7 patients through a left thoracotomy without CPB. The results were generally favorable, with postoperative angiograms demonstrating graft patency in 4 of 5 patients. Archer and co-workers [11] reported an experience of 191 patients undergoing single-vessel CABG without CPB, of whom 15 had reoperations. They documented a low perioperative and late mortality rate as well as decreased blood requirements in patients operated on without CPB. Their perioperative myocardial infarction rate for LAD bypass was 18.7%, and for this reason they abandoned the technique for isolated LAD bypass but thought the technique proved particularly useful after failed angioplasty of the RCA.

Buffolo and associates [12] reported 160 patients undergoing primary CABG without CPB with an acceptable mortality of 3.1% and a myocardial infarction rate of 2.5%. Forty-one unselected patients underwent postoperative coronary arteriography, and 84% of grafts restudied were patent. Laborde and colleagues [13] reported 38 patients undergoing CABG without CPB, including 35 having left ITA to LAD bypass grafts. There were no operative deaths and no perioperative myocardial infarctions, but no follow-up arteriography was done.

Benetti and associates [14] recently published a 12-year experience using this technique in 700 patients. The percentage of patients operated on in this series without CPB increased over the time frame of the study and reached 84% of their total coronary bypass experience in 1989. They documented a low morbidity (4%) and mortality (1%) rate. Only 10% of the patients required blood products, and 91% of patients were extubated immediately postoperatively. Hospital costs were significantly reduced in this group [15]. Fifty-four patients underwent repeat coronary angiography within 1 month postoperatively. Vein graft and ITA patency rates were 93% and 87.5%, respectively.

It is unclear from Benetti and associates' [14] report what percentage of patients had multivessel coronary disease, specifically diseased circumflex branches. Although this report describes successful revascularization of the Cx, bypass of the posterolateral branches of the Cx is not possible through a median sternotomy using this technique. As suggested in an accompanying editorial [16], either this group had incomplete revascularization or

the patient population is clearly different from that seen in the United States.

Previous reports fail to mention the utility of this technique in selected patients requiring reoperative CABG. Reoperative CABG without CPB requires less operating time and a shorter postoperative hospital stay, which translates into a reduction in hospital costs. There were fewer bleeding complications with this technique as almost one third of patients required no blood products and no patient was reexplored for excessive mediastinal hemorrhage. Although construction of distal anastomoses on the beating heart is technically more demanding and requires a short period of coronary occlusion, the observed incidence of postoperative myocardial infarction was low (1.8%).

Contrary to other reports, we have not found observation of the hemodynamic response to coronary occlusion beneficial in predicting the ability to perform a satisfactory and safe distal anastomosis. Experience with percutaneous transluminal coronary angioplasty has shown that most patients can safely tolerate brief periods of coronary occlusion. The factors that determined the ability to safely perform a technically satisfactory distal anastomosis were a coronary artery diameter at the anastomotic site of 2 mm or greater and satisfactory hemodynamics with the cardiac retraction required for exposure. Given these limitations, the technique has proved useful in selected patients requiring isolated reoperative revascularization of the RCA, Cx, and LAD using vein grafts. Hemodynamic intolerance to coronary manipulation required for grafting of the posterior descending branch of the RCA usually mandates CPB and obviates consideration of the technique. We avoid this technique when grafting a small LAD with a small ITA. Although the patients who underwent repeat coronary angiography were a select group biased toward those with recurrent symptoms, graft patency rates (90%) were comparable with reported patency rates for grafts placed using standard techniques with CPB and cardioplegic arrest.

Despite certain technical limitations, this method has proved quite useful in several situations deserving further mention. Three patients underwent successful emergent reoperative revascularization to a dominant Cx system through a left thoracotomy after a failed percutaneous transluminal coronary angioplasty. In one of these patients a standard reoperative approach through a median sternotomy would have potentially jeopardized a patent in situ right ITA to LAD graft. This approach greatly lessened that risk. In 2 other patients a left thoracotomy approach for isolated Cx repeat revascularization proved safe and expedient: 1 patient with a prior mitral valve replacement and patent grafts to the RCA and LAD and a second patient with unstable angina, a left ventricular ejection fraction of 0.16, and a prior history of a radical mediastinal tumor resection with subsequent mediastinal irradiation. Other situations where this technique proved beneficial included reoperation on a patient of the Jehovah's Witness faith and 1 patient with a prior cerebrovascular accident and a heavily diseased and calcified ascend-

ing aorta where left ITA to LAD grafting without CPB served as yet another "no touch" technique to minimize the risk of stroke [17].

Modifications in all aspects of the coronary reoperation will continue to evolve as surgeons are confronted by an ever-increasing number of patients requiring reoperative revascularization. Reoperative CABG without CPB is yet another technique that allows the operation to be tailored to the needs of the individual patient. It should be emphasized that this technique is no panacea, but in highly selected patients reoperative CABG can be performed safely and effectively without CPB.

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Pentoxifylline Decreases Cyclosporine-Induced Renal Endothelin Release and Vasoconstriction

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Cyclosporine (CSA) causes an acute vasoconstriction of renal artery and a significant increase in renal endothelin release. Pentoxifylline, a vasodilator, has been suggested to prevent CSA toxicity. To study the effect of pentoxifylline treatment on CSA-related vasoconstriction and endothelin release, a model of renal autoperfusion in the dog was used. Oral pentoxifylline at the dose of 400 mg three times daily for 3 days was given to 15 dogs. Pure powder CSA (10 mg) was injected into the isolated renal artery perfused at constant flow; changes in perfusion pressure reflected variations in vascular resistance. In the pentoxifylline-treated group (15 dogs), the infusion of

CSA caused an average increase of 27 ± 8 mm Hg in renal perfusion pressure, compared with 60 ± 10 mm Hg in a control group of 8 untreated animals ($p \leq 0.05$). Plasma concentration of endothelin in the renal vein increased from an average of 1.2 ± 0.2 pg/mL before to 2.4 ± 0.5 pg/mL after CSA administration ($p \leq 0.05$) in the control group, whereas it did not change significantly in the pentoxifylline-treated group. Thus, oral pretreatment with pentoxifylline significantly decreased the renal vasoconstriction and endothelin release due to CSA administration.

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Cyclosporine (CSA) is currently the drug of choice for immunosuppression after solid organ transplantation. Hypertension and renal failure are the two most common and severe complications due to CSA after transplantation. The precise mechanism of CSA vascular toxicity is not yet fully understood. However, it has been shown that CSA causes an acute vasoconstriction of renal arteries [1-3], which could be responsible, at least partly, for the CSA side effects observed in clinical transplantation. Several mechanisms have been suggested to explain the effects of CSA on the arterial wall, including an increase in endothelin release from the renal vessels [1] and stimulation of the adrenergic system [4]. The latter has also been found in clinical studies [5, 6]. Recently, Bianco and associates [7, 8] have suggested that oral administration of pentoxifylline, a potent vasodilator, in patients undergoing bone marrow transplantation could significantly decrease renal failure due to CSA.

The goal of the present study was to evaluate the effect of pretreatment with pentoxifylline on the renal arterial vasoconstriction response to CSA.

Material and Methods

The study was performed in 23 dogs weighing 20 to 33 kg, anesthetized with pentobarbital (30 mg/kg intravenously) and artificially ventilated at 10 to 12 cycles/min with a Harvard ventilator. After heparinization (3 mg/kg), the left iliac artery and the left renal artery and vein were isolated. A cannula was introduced retrograde into the

iliac artery and connected to a circuit tubing including a heat exchanger, an occlusive roller pump, and a depulsator. Autologous blood maintained at 37°C was pumped at constant flow into the isolated renal artery after cannulation and proximal ligation of the artery at the origin from the aorta. The ipsilateral renal vein was cannulated for renal blood sampling.

The perfusion flow of the left renal artery was adjusted by controlling the pump speed at the beginning of the experiment to obtain a mean renal perfusion pressure equal to the mean aortic pressure. Changes in renal perfusion pressure therefore reflected changes in renal arterial resistance. Perfusion pressure was measured from the arterial line just proximal to the renal inflow cannula.

Arterial blood samples were obtained regularly throughout the experiment for blood pH, oxygen tension, and carbon dioxide tension measurements. Blood pH was maintained between 7.3 and 7.4 by ventilation adjustment and bicarbonate infusion as needed.

Drugs were infused directly into the renal inflow, proximal to the insertion of the renal artery cannula and to the site of perfusion pressure monitoring. Drugs were injected over a period of 10 minutes, and changes in perfusion pressure were recorded throughout the period of infusion. Between injections, the renal perfusion pressure was allowed to return to the baseline mean aortic pressure for at least 10 minutes. Typically, perfusion pressure reached a plateau 5 to 9 minutes after the beginning of CSA infusion and persisted 5 minutes or more after the end of infusion. The plateau level was recorded as the maximal effect of the drug on renal perfusion pressure.

Nitroglycerin (5 mg) was administered at the beginning

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and at the end of each experiment to test the reactivity of renal arteries. Autologous blood alone was also injected to test reactivity to the vehicle. Pure powder CSA (Sandoz Canada, Montreal, Canada) was dissolved into autologous blood (60 mL) and injected at the dose of 10 mg. At the end of each CSA infusion, renal venous blood samples were withdrawn for determinations of CSA serum level by the fluorescence polarization immunoassay technique [9].

A group of 15 dogs was treated with oral pentoxifylline (Trental; Hoechst Canada, Montreal, Canada) at the dose of 400 mg three times daily during 3 days before the experiment. The effect of CSA on renal vascular resistance was then studied according to the protocol described. Plasma concentration of endothelin was also measured in 9 of these dogs, from peripheral venous blood sampling before the pentoxifylline treatment was started and in the renal vein before and after administration of CSA during the experiment. Endothelin-1 plasma concentration was measured by radioimmunoassay according to a method previously described [1].

Another group of 8 dogs studied without pentoxifylline pretreatment served as the control group. Plasma concentration of endothelin was measured in renal venous blood before and after CSA injection in this group.

The data are presented as mean changes in renal perfusion pressure, standard error of the mean, and 95% confidence interval (CI). Changes in perfusion pressure were analyzed by Student's paired and unpaired *t* test, and changes in endothelin levels were analyzed by Student's paired *t* test and by analysis of variance. The level of statistical significance was established at 95%. All animals were treated in accordance with the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH publication No. 85-23, revised 1985).

Results

In the group of 15 dogs pretreated with oral pentoxifylline, nitroglycerin injection caused an average decrease of 44 ± 7 mm Hg (95% CI, 29–59 mm Hg; $p \leq 0.05$) in renal perfusion pressure, indicating good vascular reactivity.

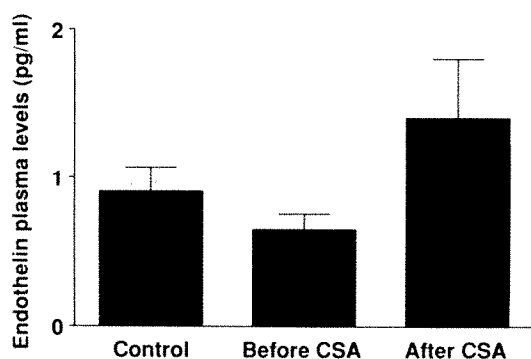


Fig 1. Plasma levels of endothelin before pentoxifylline pretreatment, before and after injection of 10 mg of cyclosporine (CSA) in dogs. No changes in endothelin concentration were found (not significant by analysis of variance).

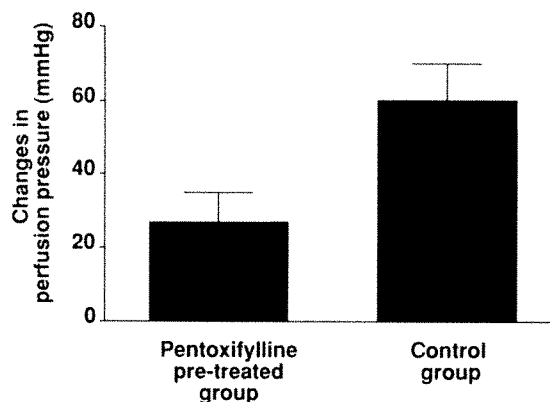


Fig 2. Increases in renal perfusion pressure with injection of 10 mg of cyclosporine in the pentoxifylline-pretreated group ($n = 15$) and the control group ($n = 8$). The difference in pressure increase is significant ($p \leq 0.05$).

Basal perfusion pressure averaged 123 ± 6 mm Hg before and 78 ± 5 mm Hg after nitroglycerin injection. Infusion of 60 mL of autologous blood did not cause any significant changes in perfusion pressure (7 ± 4 mm Hg).

Infusion of 10 mg of CSA caused an average increase of 27 ± 8 mm Hg (95% CI, 10–44 mm Hg; $p \leq 0.05$) in renal perfusion pressure from 105 ± 5 mm Hg to 132 ± 11 mm Hg with CSA serum levels averaging 360 ± 116 nmol/L at the end of injection. The plasma concentration of endothelin averaged 0.9 ± 0.2 pg/mL before pentoxifylline pretreatment, 0.7 ± 0.1 pg/mL immediately before CSA injection, and 1.3 ± 0.4 pg/mL after injection of CSA, differences that were not significant (Fig 1).

In the control group (8 dogs), nitroglycerin injection caused an average decrease of 61 ± 5 mm Hg (95% CI, 50–73 mm Hg; $p \leq 0.05$) in renal perfusion pressure. Injection of 10 mg of CSA caused an average increase of 60 ± 10 mm Hg (95% CI, 36–84 mm Hg; $p \leq 0.05$) in renal perfusion pressure, from 93 ± 5 mm Hg to 152 ± 10 mm Hg. The difference in the response of the control dogs from that of the pentoxifylline-pretreated group was statistically significant (Fig 2). The serum levels of CSA averaged 603 ± 161 nmol/L at the end of CSA injection, a nonsignificant difference from the pretreated group. The plasma concentration of endothelin in the renal vein averaged 1.2 ± 0.2 pg/mL before and 2.4 ± 0.5 pg/mL after CSA administration, a significant increase in release ($p \leq 0.05$) (Fig 3).

Comment

Clinical and experimental studies have shown that CSA causes a significant increase in renal arterial resistance at serum levels within the therapeutic range used in clinical transplantation [1–3]. Infusion of CSA has also been shown to increase significantly the renal release of endothelin [1], a potent endothelium-dependent vasoconstrictor peptide released in the renal vessels [1, 4, 10–12]. In vitro, CSA stimulates the secretion of endothelin by renal tubular and endothelial cells [13, 14]. Marked increases in plasma concentration of endothelin have been found in a

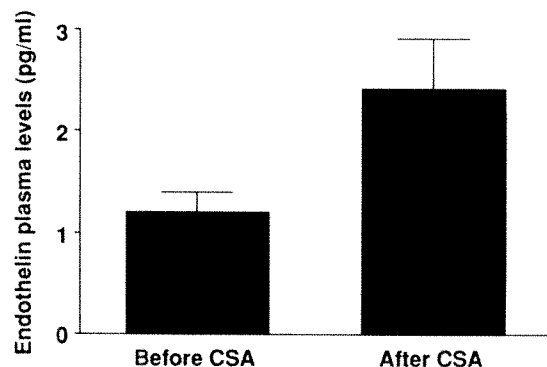


Fig 3. Plasma concentrations of endothelin before and after injection of 10 mg of cyclosporine (CSA) in the control group (8 dogs). A significant increase in endothelin concentration was obtained with CSA injection ($p \leq 0.05$).

small group of patients after liver transplantation [15]. These pieces of evidence suggest that CSA increases the endothelin release from renal endothelial cells, and that the resulting vasoconstrictive effect may play a key role in CSA nephrotoxicity and hypertension.

Pentoxifylline, a xanthine derivative with multiple effects on circulating blood cells, also exerts a potent vasodilator effect by increasing the intracellular level of adenosine 3',5'-cyclic monophosphate and by preventing the production and the effect of thromboxanes [16, 17]. In experimental studies, pentoxifylline was shown to prevent the hypoxia-related changes in renal function of transplanted kidneys [18], improve the clinical course and survival of acute renal failure [19], and reduce cyclosporin-induced nephrotoxicity in the rat [20].

In a recent clinical nonrandomized study, Bianco and associates [7] found that pentoxifylline could prevent cyclosporin toxicity in bone marrow transplant patients, as a significant decrease in the incidence of renal failure among patients treated with pentoxifylline was observed.

The results of the present study support the hypothesis of Bianco and associates. Oral pretreatment with pentoxifylline resulted in a decrease in renal vasoconstriction caused by CSA in a model of renal autoperfusion in the dog. Pentoxifylline pretreatment also prevented the increase in renal endothelin release caused by CSA, suggesting that the preventive action of pentoxifylline on CSA-induced changes in renal vascular resistance could be related to the latter mechanism. Serum levels of CSA were higher in the control group of animals; the difference could result from an incomplete dilution of CSA in the autologous blood or from an interaction between the two drugs. Further studies will clarify this aspect.

In conclusion, oral pretreatment with pentoxifylline prevents, at least partly, the renal vasoconstriction caused by CSA, and this effect may be due to inhibition of endothelin release, which therefore could be responsible for renal toxicity of CSA. Clinical studies will be needed to confirm the preventive effect of pentoxifylline on CSA-related nephrotoxicity. Oral pentoxifylline administered to transplant patients with CSA could become an approach to prevent the renal vascular toxicity of CSA.

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Dynamic Cardiomyoplasty in Chronic Left Ventricular Failure: An Experimental Model

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Dynamic cardiomyoplasty continues to attract interest as a therapeutic option in the management of heart failure. In a large animal model of ischemic heart failure, we have compared dynamic cardiomyoplasty with both adynamic cardiomyoplasty and a control group. Heart failure was induced by coronary artery ligation in sheep, and under the same anesthetic dynamic cardiomyoplasty ($n = 5$), adynamic cardiomyoplasty ($n = 4$), or no further procedure was performed ($n = 5$). After recovery the animals were housed for a further 3 months. The dynamic cardiomyoplasty underwent a recognized muscle transformation protocol during this period. At terminal studies, the animals were hemodynamically assessed, both under baseline conditions and after colloid volume loading. The data at baseline were compared with unpaired t tests, and the function curves created by volume

loading were compared by analysis of variance. Although the changes at baseline were small, there were highly significant improvements in the function curves in the dynamic cardiomyoplasty group when the stimulators were turned on compared with stimulators off ($p = 0.005$ for cardiac output; $p = 0.035$ for left ventricular end-diastolic pressure; $p = 0.002$ for pulmonary artery capillary wedge pressure; $p = 0.004$ for stroke volume; and $p = 0.003$ for cardiac power). There were also significant improvements in indices of cardiac performance when the dynamic cardiomyoplasty group was compared with both the control and adynamic cardiomyoplasty groups. We conclude that there is experimental evidence that cardiomyoplasty augments cardiac function in a model of chronic left ventricular failure.

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A major and continuing fault throughout the literature on experimental cardiomyoplasty is the lack of an effective and reliable chronic heart failure model. The result is that the majority of experimental studies published to date have been either acute studies using muscle that has not been previously transformed [1], or studies using muscle that has been transformed in situ and moved at the time of the operation with the animals studied acutely at that time. The final group of studies are those in which the operation has been performed and the animals allowed to recover and undergo a muscle transformation protocol with an acute type of study after this muscle transformation period [2].

These studies are criticized either on the grounds that the acutely operated muscle will produce more power with a much faster twitch than the transformed muscle [3], before it very rapidly fatigues, or that the acutely failing ventricle after administration of propranolol or similar agents is not representative of the clinical situation. Attempts to overcome these criticisms have focused on using chronically cardiotoxic agents such as the anthracycline antibiotic doxorubicin hydrochloride (Adriamycin; Adria Laboratories, Dublin, OH), the tricyclic antidepressant

imipramine, or long-term β -adrenoceptor blockade. Although doxorubicin produces an effect similar to a dilated cardiomyopathy, the toxicity and narrow "therapeutic" window have resulted in very high mortality rates in experimental cardiomyoplasty. The cost of these agents and the hematological monitoring that they need also inhibits their use.

Theoretical worries about the effects of long-term β -adrenoceptor blockade on skeletal muscle have also been raised in relation to dynamic cardiomyoplasty. There is experimental evidence that the training adaptations of skeletal muscle are impaired by long-term β -adrenoceptor blockade and that the effects depend on both the fiber type studied and the type of β -adrenoceptor antagonist used [4].

It was for these reasons that this study of dynamic cardiomyoplasty in an ischemic model of left ventricular (LV) failure was planned. We have previously shown that the sheep model of LV aneurysm produces hemodynamically significant LV failure [5].

Material and Methods

Three groups of animals were prepared. The first group were the animals with pure LV aneurysms (group 1). The second group of animals (group 2) underwent cardiomyoplasty after coronary ligation, but without the implantation of the cardiomyostimulator and leads (adynamic cardiomyoplasty). The third group (group 3) underwent cardiomyoplasty after coronary ligation with the simulta-

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neous implantation of the cardiomyostimulator and leads (dynamic cardiomyoplasty). In both groups 2 and 3, the cardiomyoplasty was performed at the same operation as coronary ligation, after the animals had hemodynamically stabilized. All group 3 animals underwent a standard muscle pacing protocol over 12 weeks, by the end of which they were receiving 5-V pulse trains of 240-ms duration, with a pulse frequency of 33 Hz and at a 1:1 relation with the cardiac R wave. This protocol has been described in detail elsewhere [6]. The other animals were housed for the same time before undergoing their terminal studies (groups 1 and 2).

Management of Experimental Animals

All animals received humane care in accordance with guidelines published by the National Society for Medical Research (Principles of Laboratory Animal Care) and by the National Institutes of Health ("Guide for Care and Use of Laboratory Animals"; NIH publication No. 85-23, revised 1985). The project was licensed and performed under the supervision of H. M. Inspector from the Home Office.

Operative Techniques

CREATION OF THE MYOCARDIAL INFARCT. Our anesthetic and operative management has been previously described [5], and creation of the myocardial infarct was based on a previously described method [7].

PREPARATION OF THE LATISSIMUS DORSI FLAP. In those animals in which a latissimus dorsi flap was raised, preparation of the latissimus dorsi flap followed immediately after the coronary artery ligation had been performed. The skin incision of the thoracotomy was extended further posteriorly and deepened with a scalpel through the superficial platysma muscle to the latissimus dorsi. Skin flaps were reflected both cranially and caudally until the whole of the muscle had been released over its subcutaneous aspect. Next the anterior border was completely mobilized, followed by the posterior border. The fibrous origin from the ribs was then divided and hemostasis on the chest wall and subcutaneous flaps secured. The muscle was then reflected anteriorly, allowing the common insertion with teres major to be divided with further mobilization of the latissimus dorsi flap. To avoid neurovascular damage, in this experimental model, the tendinous insertion onto the humerus was not divided.

The intercostal muscles over the third rib were divided and a 4-cm anterior arc of the third rib together with the periosteum was excised. The latissimus dorsi was then passed into the chest through this space. Pacing leads (SP5528; Medtronic Ltd, Maastricht, Holland) were attached (group 3 only) and the muscle passed over the front of the left ventricle. The muscle was secured in place by bringing the pericardial edges together over the front of the muscle. In addition the muscle was sewn to the diaphragmatic surface of the pericardium, ensuring stability during the earlier onset of the pacing protocol. In

group 3 animals the cardiomyostimulator (SP1005; Medtronic Ltd) was inserted into a subcutaneous pocket with the pacing leads being routed so that they did not lie directly under the incision.

Postoperative Study Protocol

Hemodynamic studies were performed at three points: before coronary artery ligation, 1 hour after coronary artery ligation, and 3 months after the initial operation. Three months after the initial operation the animals were reanesthetized using exactly the same protocol and reinstrumented in the same way as before.

Hemodynamic measurements were taken after the animals were anesthetized, ventilated, and fully instrumented, with their chests closed and under the same conditions as their preinfarction studies. Recordings were made at baseline and then after 500-mL boluses of colloid plasma expander (Gelofusine; Consolidated Chemicals Ltd, Wrexham, Wales). Measurements were made in group 3 with the pacemaker off after the animals had stabilized for 10 minutes, and repeated with the pacemaker on, using the parameters described above, after a further period of 10 minutes of stabilization. In groups 1 and 2 measurements were made at baseline and after 500-mL boluses of colloid plasma expander, with 10-minute stabilization periods after fluid loading and before recordings were made.

Once the hemodynamic study was completed, the animals were sacrificed under anesthesia for postmortem examination of their hearts.

Statistical Methods

The comparisons between the groups for preinfarction, postinfarction, and baseline terminal studies have been performed with unpaired two-tailed *t* tests. The initial comparisons between the groups for the function curves derived from volume loading at the terminal studies have been made with repeated-measures analysis of variance (ANOVA). Differences between groups at specific points on the volume loading curves were then inspected using paired or unpaired two-tailed *t* tests as appropriate for the groups under comparison.

Results

There were 6 animals suitable for study with adequate aneurysms in the dynamic cardiomyoplasty group (group 3), 5 animals suitable for study with adequate aneurysms in the adynamic cardiomyoplasty group (group 2), and 6 animals with aneurysms alone (group 1). Insurmountable technical problems during the terminal studies, while the animals were anesthetized and after monitoring lines had been inserted, resulted in loss of major elements of the data from 2 animals. These were 1 each from groups 1 and 3.

One animal from group 2 died very rapidly after the induction of anesthesia and while the monitoring lines were being inserted. Full resuscitative measures were attempted, but these were unsuccessful and it was not

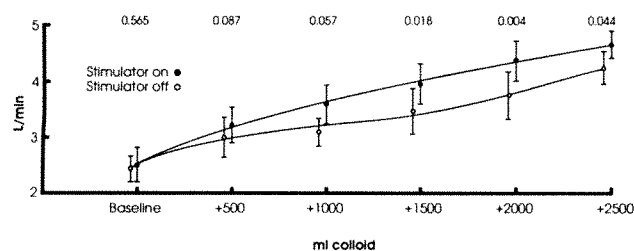


Fig 1. Graph of cardiac output against volume of colloid transfused during the terminal studies in group 3. Numerical values are the *p* values for the two-tailed paired *t* test at each point.

possible to obtain any hemodynamic data from this animal. There were no cardiomyostimulator- or lead-related problems in this series, and only one minor wound infection that settled with conservative management.

Data were therefore available for analysis from 5 of the 6 animals in group 1, 4 of the 5 animals in group 2, and 5 of the 6 animals in group 3.

The preinfarction, 1 hour postinfarction, and baseline 3-month postoperation measurements were first compared for the following indices: heart rate, systolic aortic pressure, diastolic aortic pressure, mean aortic pressure, systolic LV pressure, end-diastolic LV pressure, systolic pulmonary artery pressure, diastolic pulmonary artery pressure, mean pulmonary artery pressure, mean pulmonary artery capillary wedge pressure, right atrial pressure, cardiac output, positive time derivative of LV pressure (dp/dt), negative LV dp/dt , stroke volume, stroke work, cardiac power, systemic vascular resistance, and pulmonary vascular resistance.

Left ventricular end-diastolic pressure was measured from the LV pressure curve, and was taken to occur at the beginning of the rapid upstroke of the dp/dt [8].

Having done this, the function curves created by plotting an index on the *y* axis against the volume transfused on the *x* axis were then compared for the same set of indices. Representative function curves are shown in Figures 1 to 5; for economy of space all the curves are not shown. The *p* values for the various significance tests are shown in Tables 1 to 7.

Preinfarction and Postinfarction Data

In the comparison between groups 1 and 3, their weights were similar as were their initial hemodynamic measure-

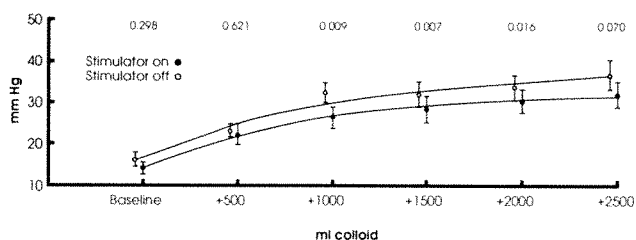


Fig 2. Graph of end-diastolic left ventricular pressure against volume of colloid transfused during the terminal studies in group 3. Numerical values are the *p* values for the two-tailed paired *t* test at each point.

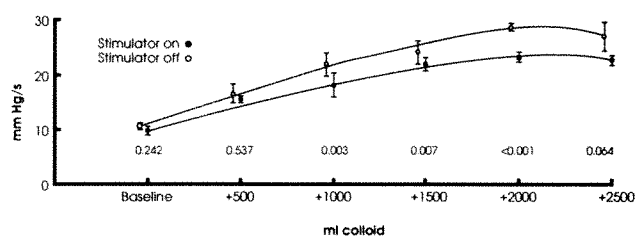


Fig 3. Graph of pulmonary artery wedge pressure against volume of colloid transfused during the terminal studies in group 3. Numerical values are the *p* values for the two-tailed paired *t* test at each point.

ments. There are two exceptions to this, the differences in pulmonary artery capillary wedge pressures (9.6 ± 0.83 mm Hg for group 1 and 5.8 ± 1.04 mm Hg for group 2; $p = 0.032$) and the differences in right atrial pressures (5.0 ± 0.49 mm Hg for group 1 and 1.6 ± 0.92 mm Hg for group 2; $p = 0.005$). There was just one statistically significant difference in the 1-hour postinfarction data, with the pulmonary artery diastolic pressure being 15.0 ± 2.61 mm Hg for group 1 and 13.2 ± 1.71 mm Hg for group 2 ($p = 0.049$).

Likewise, in the comparison between groups 1 and 3, their weights were similar as were their initial hemodynamic measurements. In the immediate postinfarction period there was no difference between groups 1 and 3. This is important as it implies that an equality of infarct area was achieved and therefore that the aneurysms, and hemodynamic impairment, produced were similar in the two groups.

Comparing the control data for the groups 2 and 3, there were small differences before infarction in the pulmonary artery capillary wedge pressure and the right atrial pressure. For group 2, pulmonary artery capillary wedge pressure was 5.8 ± 1.04 mm Hg, and for group 3, it was 6.8 ± 1.86 mm Hg ($p = 0.027$). For group 2, right atrial pressure was 1.6 ± 0.92 mm Hg, and for group 3, it was 3.4 ± 1.43 mm Hg ($p = 0.002$). These differences were abolished after coronary artery ligation, and by 1 hour after coronary artery ligation there were no significant differences between these two groups. These results confirm that these groups were all comparable with each other at the outset of their recovery phase and muscle transformation protocol.

Baseline Terminal Studies

A major criticism of clinical cardiomyoplasty has been the discordance between the patients' reported improvement

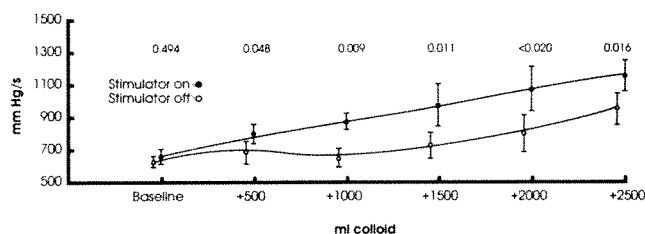


Fig 4. Graph of peak positive left ventricular dp/dt against volume of colloid transfused during the terminal studies in group 3. Numerical values are the *p* values for the two-tailed paired *t* test at each point.

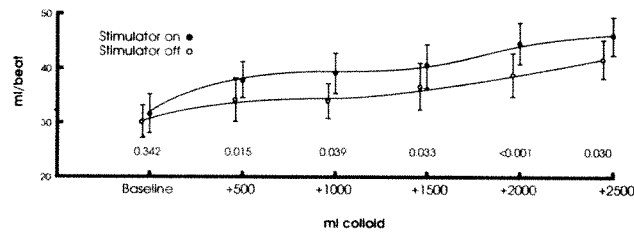


Fig 5. Graph of stroke volume against volume of colloid transfused during the terminal studies in group 3. Numerical values are the *p* values for the two-tailed paired *t* test at each point.

in symptomatology and their apparent lack of improvement in noninvasive indices of LV function at rest. Indeed, this is confirmed in this experimental model, where if we consider the baseline differences at the terminal studies, it can be seen that the only differences between groups 1 and 3 (see Table 2) lies in a slower heart rate in group 3, both with the cardiomyostimulator turned off (102.2 ± 3.43 versus 88.4 ± 5.17 beats/min; $p = 0.024$) and when it is turned on (102.2 ± 3.43 versus 79.6 ± 4.42 beats/min; $p = 0.006$).

There are similarly no differences between groups 1 and 2 (see Table 1) or between groups 2 and 3 at the baseline terminal studies (see Table 3), although there is a ten-

Table 1. Comparison by Two-Tailed Unpaired *t*-Tests of the Baseline 3-Month Postinfarction Data Between the Animals With Left Ventricular Aneurysms (group 1) and Those With Adynamic Cardiomyoplasty (group 2)

Variable	<i>p</i> Value
Heart rate	0.725
AoS	0.941
AoD	0.598
AoM	0.714
LVS	0.516
LVEDP	0.686
PAS	0.255
PAD	0.163
PAM	0.193
PACW	0.445
RA	0.491
Q mean	0.490
+LVdp/dt	0.931
-LVdp/dt	0.695
Stroke volume	0.637
Stroke work	0.813
Power	0.748
SVR	0.435
PVR	0.182

AoD = diastolic aortic pressure; AoM = mean aortic pressure; AoS = systolic aortic pressure; +LVdp/dt = maximum positive rate of change of left ventricular pressure; -LVdp/dt = maximum negative rate of change of left ventricular pressure; LVEDP = end-diastolic left ventricular pressure; LVS = systolic left ventricular pressure; PACW = pulmonary artery capillary wedge pressure; PAD = diastolic pulmonary artery pressure; PAM = mean pulmonary artery pressure; PAS = systolic pulmonary artery pressure; PVR = pulmonary vascular resistance; Q mean = mean cardiac output; RA = right atrial pressure; SVR = systemic vascular resistance.

Table 2. Comparison by Two-Tailed Unpaired *t*-Tests of the Baseline 3-Month Postinfarction Data Between the Animals With Left Ventricular Aneurysms Alone (group 1) and the Animals Undergoing Dynamic Cardiomyoplasty (group 3) With the Stimulators Off and the Stimulators On

Variable	Stimulator Off	Stimulator On
Heart rate	0.024	0.006
AoS	0.916	0.858
AoD	0.802	0.806
AoM	0.839	0.809
LVS	0.829	0.813
LVEDP	0.525	0.200
PAS	0.914	0.787
PAD	0.334	0.270
PAM	0.513	0.417
PACW	0.911	0.662
RA	0.504	0.399
Q mean	0.796	0.977
+LVdp/dt	0.909	0.649
-LVdp/dt	0.689	0.924
Stroke volume	0.206	0.173
Stroke work	0.369	0.285
Power	0.507	0.436
SVR	0.542	0.552
PVR	0.192	0.127

Abbreviations are as in Table 1.

dency for the heart rate to be slower in group 3 than in group 2 (stimulator off: 106 ± 7.99 versus 88.4 ± 5.17 beats/min; $p = 0.076$; stimulator on: 106 ± 7.99 versus 79.6 ± 4.42 beats/min; $p = 0.056$).

Table 3. Comparison by Two-Tailed Unpaired *t*-Tests of the Baseline 3-Month Postinfarction Data Between the Animals With Adynamic Cardiomyoplasty (group 2) and Those Undergoing Dynamic Cardiomyoplasty (group 3) With the Stimulators Off and the Stimulators On

Variable	Stimulator Off	Stimulator On
Heart rate	0.076	0.056
AoS	0.984	0.921
AoD	0.733	0.696
AoM	0.825	0.838
LVS	0.695	0.678
LVEDP	0.477	0.327
PAS	0.256	0.285
PAD	0.329	0.371
PAM	0.294	0.331
PACW	0.368	0.284
RA	0.162	0.131
Q mean	0.674	0.596
+LVdp/dt	1.000	0.748
-LVdp/dt	0.826	0.723
Stroke volume	0.187	0.150
Stroke work	0.336	0.256
Power	0.776	0.653
SVR	0.849	0.835
PVR	0.413	0.60

Abbreviations are as in Table 1.

Table 4. Comparison by Analysis of Variance of the Terminal Hemodynamic Studies Between the Group of Animals Undergoing the Creation of a Left Ventricular Aneurysm Alone (group 1) and Those Undergoing Adynamic Cardiomyoplasty (group 2)

Variable	p Value
Heart rate	0.957
AoS	0.705
AoD	0.719
AoM	0.744
LVS	0.700
LVEDP	0.881
PAS	0.520
PAD	0.034
PAM	0.072
PACW	0.576
RA	0.296
Q mean	0.151
+LVdp/dt	0.701
-LVdp/dt	0.832
Stroke volume	0.433
Stroke work	0.656
Power	0.439
SVR	0.304
PVR	0.099

Abbreviations are as in Table 1.

Comment

Stress Testing Terminal Studies

If this experimental model is to be relevant and reproducible, then there has to be an element of stress testing

Table 5. Comparison by Analysis of Variance of the Terminal Hemodynamic Studies Between the Group of Animals Undergoing the Creation of a Left Ventricular Aneurysm Alone (group 1) and Those Undergoing Dynamic Cardiomyoplasty (group 3)

Variable	Stimulator Off	Stimulator On
Heart rate	0.006	0.007
AoS	0.908	0.929
AoD	0.935	0.925
AoM	0.921	0.927
LVS	0.943	0.900
LVEDP	0.224	0.057
PAS	0.290	0.011
PAD	0.939	0.279
PAM	0.706	0.087
PACW	0.236	0.023
RA	0.545	0.111
Q mean	0.843	0.504
+LVdp/dt	0.736	0.396
-LVdp/dt	0.879	0.946
Stroke volume	0.253	0.068
Stroke work	0.525	0.211
Power	0.798	0.693
SVR	0.701	0.980
PVR	0.339	0.244

Abbreviations are as in Table 1.

Table 6. Comparison by Analysis of Variance of the Terminal Hemodynamic Studies Between the Group of Animals Undergoing the Creation of an Adynamic Cardiomyoplasty (group 2) and the Group of Animals Undergoing Dynamic Cardiomyoplasty (group 3)

Variable	Stimulator Off	Stimulator On
Heart Rate	0.132	0.135
AoS	0.516	0.496
AoD	0.592	0.574
AoM	0.597	0.584
LVS	0.745	0.777
LVEDP	0.321	0.134
PAS	0.201	0.023
PAD	0.139	0.018
PAM	0.128	0.015
PACW	0.088	0.008
RA	0.099	0.010
Q mean	0.264	0.067
+LVdp/dt	0.888	0.219
-LVdp/dt	0.911	0.824
Stroke volume	0.136	0.047
Stroke work	0.263	0.093
Power	0.421	0.119
SVR	0.441	0.236
PVR	0.425	0.326

Abbreviations are as in Table 1.

included. The New York Heart Association classification is a clinical assessment based on a patient's reported exercise tolerance and for this reason cannot be directly compared with animal pathophysiology. There is an increasing awareness in the investigation of clinical heart

Table 7. Repeated-Measures Analysis of Variance Comparison Between the Cardiomyostimulator Off and Cardiomyostimulator On Measurements for Group 3 After Volume Loading

Variable	p Value
Heart rate	0.960
AoS	0.814
AoD	0.911
AoM	0.917
LVS	0.694
LVEDP	0.035
PAS	0.026
PAD	0.141
PAM	0.042
PACW	0.002
RA	0.021
Q mean	0.005
+LVdp/dt	0.003
-LVdp/dt	0.240
Stroke volume	0.004
Stroke work	0.008
Power	0.003
SVR	0.147
PVR	0.873

Abbreviations are as in Table 1.

failure that exercise testing and assessment of exercise hemodynamics and metabolism is highly significant. Obviously in the anesthetized and instrumented sheep this is difficult, and therefore we elected to study these animals by worsening their heart failure by volume loading. This is justified as normal humans do not show an increase in preload indices during exercise, whereas patients with heart failure will show significant increases in pulmonary artery capillary wedge pressures [9].

Volume loading to a total of 2,500 mL of colloid plasma expander is a severe challenge, particularly to an animal of only 40 kg, even without an already impaired heart. There was noticeable tissue edema by the end of the procedure, and endotracheal suction often produced frothy fluid after approximately 2,000 mL of plasma expander had been transfused. Hemodilution was apparent, with marked decreases in hemoglobin levels by the end of the procedure.

To create true Frank-Starling curves it would be necessary to plot LV end-diastolic volume against the systolic indices at a constant heart rate. To obtain a constant heart rate would have required inserting a temporary endovenous pacing wire, without x-ray screening. Although this is feasible, particularly with a pacing Swan-Ganz catheter, it would still have been necessary to insert a second pulmonary artery catheter. Furthermore, the higher heart rate required presented the risk of inducing Wenckebach of the cardiomyostimulator, which would have added a further variable to the study. For these reasons we elected to leave heart rate uncontrolled.

Comparison of Groups 1 and 2

If we consider first the comparison of the function curves from group 1 with those from group 2 (see Table 4), then we see that only the curves for diastolic pulmonary artery pressure, with a p value by ANOVA of 0.034, are significantly different. Furthermore, there is little sign that any of the other curves would be likely to be significantly different if the numbers of animals in each group were increased. It is apparent from this that simply applying an unstimulated muscle wrap to an infarcting area of the left ventricle, in this model, does not improve the function of the remaining myocardium.

Comparison of Cardiomyostimulator Off Against On in Group 3

If the function curves for the various indices against volume loading are compared within group 3 (see Table 7), the dynamic cardiomyoplasty group, then it can be seen that comparing the cardiomyostimulator on with the cardiomyostimulator off shows changes in the indices of preload (LV end-diastolic pressure, pulmonary artery capillary wedge pressure, mean pulmonary artery pressure, right atrial pressure) and the derived indices of function (stroke volume, stroke work) while there is little or no change in the direct indices of systolic function (systolic aortic pressure, systolic LV pressure). Left ventricular dp/dt shows a significant change, whereas heart rate does not.

If some of these curves are considered in more detail, there is a definite increase in cardiac output after the

cardiomyostimulator is activated. This is clearly seen from the curve in Figure 1, and is of greatly increased significance with the decrease in indices of preload (see Figs 2, 3). The p value by ANOVA is 0.005. As would be expected, there is a progressive increase in cardiac output as the animals were volume loaded. Figure 1 shows the curves, with the significance values by paired two-tailed t tests entered onto the curves. It is apparent from this figure that there is an increasing effect from the cardiomyoplasty as the animals are volume loaded, with a p value of 0.018 at +1,500 mL and 0.004 at +2,000 mL.

The changes in indices of preload have been mentioned above. The directly measured LV end-diastolic pressure shows the expected increase from its already elevated level with serial volume loading (see Fig 2). At each point the institution of muscle stimulation produces a decrease in the pressure, although this decrease is most marked in the middle of the volume loading range. Figure 2 shows the p values by a paired two-tailed t test entered onto the curves of LV end-diastolic pressure. Similarly to the cardiac output curve, significant differences can be seen at the +1,500 mL and +2,000 mL points, with p values of 0.007 and 0.016, respectively. There is also a significant improvement at the +1,000 mL point, with a p value of 0.009.

The mean pulmonary artery capillary wedge pressure shows a similar decrease when muscle flap stimulation is instituted on top of the expected increases with volume loading. Figure 3 shows the p values by a paired two-tailed t test entered onto the curve. As would be expected, this curve is very similar to the LV end-diastolic pressure curve, in spite of being measured with a different type of transducer. The p values at +1,000 mL, +1,500 mL, and +2,000 mL are all significant, with values of 0.003, 0.007, and less than 0.001, respectively.

The curves for systolic, diastolic, and mean pulmonary artery pressure all suggest that there is a decrease in pulmonary artery pressures with cardiomyoplasty, with the curves for systolic and mean pulmonary artery pressures reaching significance at p values by ANOVA of 0.026 and 0.042, respectively.

The decrease in systemic vascular resistance is most likely to be a homeostatic mechanism to normalize arterial pressures at a constant level with the increased cardiac output, and as such is the probable explanation for the failure of the arterial pressures to increase with cardiomyoplasty.

The maximum LV dp/dt shows a consistent increase when the cardiomyostimulator was switched on, and the maximum LV dp/dt also shows a serial increase with volume loading. Figure 4 shows the significance values of two-tailed paired t tests on the curves for maximum LV dp/dt. It is interesting to note that whereas the differences from +500 mL to +2,500 mL are all significant, it is the differences at +1,000 mL and +1,500 mL that are the most prominent. This is in good agreement with the rest of the hemodynamic data.

Although the sensitivity of dp/dt to changes in preload and afterload is disputed, it is an isovolumic contractile index that is sensitive to changes in "inotropic state" [10, 11]. It is difficult from our data to determine whether the

increase in dp/dt is the primary event, or whether the increase in dp/dt is reflecting a decrease in systemic vascular resistance, which is in its own turn due to the increased cardiac output. It is clear though that there is an increase in left ventricular performance whether it is measured by the LV dp/dt , the cardiac output, or both. Recent experimental evidence in humans [12] suggests that dp/dt is independent of both preload and afterload, and therefore these animals are showing a primary improvement in LV contractility with dynamic cardiomyoplasty.

It would be reasonable to suggest that the improved ventricular function created by turning the cardiomyostimulator on leads to an improved cardiac output, a decrease in the indices of preload, and a maintenance of the arterial blood pressure by a reflex decrease in systemic vascular resistance. A beneficial side effect of this is a decrease in the subendocardial perfusion gradient (diastolic aortic pressure minus LV end-diastolic pressure) with a consequent increase in oxygen delivery to this important region.

There are a series of important indices that can be derived from these data. Stroke volume is the simplest, and this shows a significant and consistent increase with cardiomyoplasty. This reaches significance by ANOVA at a p value of 0.004. Interestingly, the highest percentage increases in stroke volume are seen in the mid and upper range of the curves. The increase with the cardiomyostimulator turned on is only 4.6% at the baseline, 10.4% at +500 mL, 15.1% at +1,000 mL, 10.6% at +1,500 mL, and 14.9% at +2,000 mL. Figure 5 shows the values for significance from the two-tailed paired t tests, and the percentage improvements noted above were all significant when the underlying data were examined.

The stroke work has been calculated using the aortic pressure data. The curves show significant increases in stroke work, with a p value by ANOVA of 0.006. This finding is to be expected from the decreases in the preload indices and the increases in cardiac output and hence stroke volume.

Cardiac power has been calculated according to the formula of Tan and associates [13]. This is a formula that has been put forward to improve the assessment of cardiac function in heart failure. The increase in cardiac power when the cardiomyostimulator is switched on is further evidence that the cardiomyoplasty is contributing to cardiac performance.

Whereas the calculated increases in stroke volume, stroke work, and cardiac power are derived measurements from the cardiac output, the increase in LV dp/dt is a directly measured index of improved ventricular contractility. It could be argued that it is unsafe to place too much reliance on a single measurement, or a series of measurements that are essentially derived from the same original measurement. It could also be argued that stroke volume, stroke work, and cardiac power are very closely related, and therefore do not lead to any increased support for the hypothesis over and above the improvement seen in cardiac output. However, the measurement of cardiac output and LV dp/dt are not significantly related. Furthermore, for all the discussion of the merits of LV

dp/dt as an index of contractility, there is no suggestion that it should increase with a decrease in LV end-diastolic pressure. Therefore the decrease in LV end-diastolic pressure seen here at the same time as an improvement in cardiac output and stroke volume is an additional and independent support for the assumption that the cardiomyoplasty is contributing to the increase in cardiac power. The similarities in behavior of pulmonary artery capillary wedge pressure and LV end-diastolic pressure are of mutual support as the two measurements are made with different systems. Therefore, each measurement supports the validity of the other.

There are now two further issues of importance, these being the differences in performance between group 3 and groups 1 and 2. Both groups 1 and 2 need to be compared with both the cardiomyostimulator off and cardiomyostimulator on data from group 3.

Comparison of Groups 1 and 3

Comparing group 1 and the cardiomyostimulator off data by ANOVA, it can be seen that the only significant difference is a lower heart rate in group 3 ($p = 0.007$ by ANOVA). When group 1 is compared with the cardiomyostimulator on data from group 3, this difference is maintained (see Table 5), and there are now significant decreases in systolic pulmonary artery pressure and pulmonary artery capillary wedge pressure. These differences have p values by ANOVA of 0.011 and 0.023, respectively. Inspection of Table 2 shows that the changes are not significant between the groups at baseline by unpaired two-tailed t tests. However, these changes become significant as the animals are volume loaded and the two curves diverge.

There are trends toward lowered LV end-diastolic pressure ($p = 0.057$ by ANOVA) and, to a lesser degree, mean pulmonary artery pressure ($p = 0.087$ by ANOVA). The curve for LV end-diastolic pressure shows a similar pattern to those of systolic pulmonary artery pressure and pulmonary artery capillary wedge pressure; however, the individual points all fail to reach significance.

Stroke volume shows a trend toward increasing, with a p value of 0.068. The p values for unpaired two-tailed t tests show a trend toward a difference between the two groups in the earlier part of the function curve. Although there are definite indicators of improved function with cardiomyoplasty when compared against the control group, the changes are not as clear as they were in the straightforward off-on studies within group 3.

Comparison of Groups 2 and 3

It is interesting that in the comparison between group 2 and group 3, although with the cardiomyostimulator off there is no difference between the two groups, differences become apparent in the comparison between group 2 and the cardiomyostimulator on data of group 3 (see Table 6). The distribution of improvement is similar to that seen in the off-on studies of group 3 itself. All the pulmonary artery pressures are lowered with the cardiomyostimulator on, the p values being 0.023 for systolic, 0.018 for diastolic, and 0.015 for mean pulmonary artery pressure. The decrease in pulmonary artery capillary wedge pres-

sure is significant at $p = 0.008$, and that of right atrial pressure at $p = 0.010$. Cardiac output tends to increase ($p = 0.067$), whereas stroke volume just reaches significance ($p = 0.047$). Stroke work is further away from significance ($p = 0.093$).

Mechanism of Improved Ventricular Performance

The improved ventricular performance cannot be solely due to a "splinting" of the heart by the latissimus dorsi muscle; if this were so then there would not be any improvement in cardiac output when the cardiomyostimulator was switched on in group 3, nor would there be a difference between groups 2 and 3.

It has also been shown from acute experiments [14] that the orientation of the wrap used in this study is an inefficient method for transferring energy from muscle contraction to mass transport of blood. Even with the most carefully constructed cardiomyoplasty, in the orientation used in this study, it is not unusual for coverage of the infarcted region with paced skeletal muscle to be incomplete. The usual explanation for the clinical improvement seen after cardiomyoplasty is that the heart is "squeezed" by the muscle wrap as it contracts. Indeed this may be so, which implies therefore that the improvements seen in cardiac performance in this model underestimate those that could be seen if the wrap were to be completed by patch extension of the muscle.

There is an alternative suggestion that at least part of the transfer of energy from the muscle to the blood stream comes about as a result of forceful displacement of the heart within the mediastinum. It is harder to visualize the exact mechanism by which this might occur, although in the model used here it was obvious that there was substantial potential for cardiac displacement to occur.

Recently, though, there has been increasing discussion that the changes in wall stress produced by the muscle wrap, in particular the decrease produced by the thickening of the ventricle, are of importance [1]. It is clear that the wall stress at the aneurysm is greatly decreased by the thickening of the wall from the 1 or 2 mm of the fibrous aneurysm to the 5 to 15 mm of the muscle-wrapped aneurysm. Presumably this will normalize the stress pattern within the contracting left ventricle, allowing mechanically more efficient contraction at a lower energy, and oxygen, consumption. Indeed, it has recently been pointed out that not only is there a very marked increase in regional wall stress index in the aneurysm itself, but the increase only declines slowly in the transition zone between the aneurysm and the remote normal myocardium [15]. However, the similarity in function curves between the adynamic myoplasty and the control group shows that simply decreasing the regional wall stress index by thickening the aneurysm with the muscle wrap does not on its own improve cardiac function.

Ventricular Relaxation

The curve for the peak negative LV dp/dt , the fastest rate at which intraventricular pressure is declining, is the best index in this study of ventricular relaxation [11, 16, 17]. There is no correlation between the use of the cardiomyostimulator and changes in the negative LV dp/dt ; indeed,

there is little change between the values at the beginning and the end of the volume loading experiment. There has been considerable concern that cardiomyoplasty could slow ventricular relaxation and therefore would inhibit ventricular filling. Certainly in this model there is no evidence for this hypothesis, although there is an important difference in this model of cardiomyoplasty: in these experiments, the wrap was incomplete, being passed over the free wall of the left ventricle and the anterior wall of the right ventricle, and around the apex. Although this allowed a model in which the animals could survive the procedure, it did not allow for direct comparison of the effects of ventricular relaxation with other models of cardiomyoplasty.

Improving the Model

This model of cardiomyoplasty probably underestimates the effect of skeletal muscle support, as the wrap is incomplete and the tendon of the latissimus dorsi was left intact, rather than being divided and sutured to a rib. It was very obvious that when the animals were anesthetized and on their sides there was a very considerable amount of shoulder movement. When the shoulder was stabilized, the arterial pressures could be seen to increase. Although all the measurements were made with the shoulder stabilized, there still remained some forelimb movement. This movement creates a variable degree of mechanical instability, with consequent inefficiency of power transfer between the working muscle and the heart. It is highly likely that the changes with institution of muscle pacing could be further improved by attention to these two points.

Conclusion

It is possible to produce a model of experimental dynamic cardiomyoplasty in chronic LV failure. Although the model we have used has mechanical limitations to energy transfer between the latissimus dorsi muscle flap and the blood stream, it has still shown highly significant improvements in indices of cardiac function. This has been seen both within the dynamic cardiomyoplasty group, when the stimulator on is compared with the stimulator off situation, and also when the stimulator on is compared with the control group and the adynamic cardiomyoplasty group. The enhancements seen under stress lend support to both the symptomatic upgrade and the improvements in indices of function, during exercise, seen in patients [18].

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Late Results After Triple-Valve Replacement With Various Substitute Valves

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The purpose of this study was to determine what influence various combinations of mechanical and bioprosthetic valves in the aortic, mitral, and tricuspid positions had on late morbidity and mortality of 40 hospital survivors of triple-valve replacement. At operation the patients ranged in age from 27 to 69 years; 73% were women. The mean postoperative follow-up interval was 8.3 years, with a total follow-up of 331 years (100% complete). At 12 months after operation, functional class decreased from 3.3 to 1.6 ($p < 0.05$), cardiac index increased from 2.0 to 2.6 L · min⁻¹ · m⁻² ($p < 0.05$), and pulmonary artery pressures decreased from 59/27 to 40/17 mm Hg ($p < 0.05$). There were no differences in preoperative variables between groups. Actuarial survival for the 40 patients (exclusive of 30-day or in-hospital mortality, which was 31%) was 78% and 74% at 5 and 10 years. At the same milestones, freedom from reoperation was 96% and 54%, freedom from combined thromboembolism and anticoagulant-related hemorrhage was 68% and 56%, and freedom from all late valve-related morbidity

and mortality was 64% and 25%. Comparison of the patients with two or more mechanical prostheses with the patients having two or more bioprostheses indicated no significant differences in actuarial freedom from late death, thromboembolic events, or anticoagulant-related hemorrhage. However the actuarial freedom from reoperation in the groups with two or more mechanical valves was lower than that of the groups with two or more bioprosthetic valves (0/10 versus 13/30; $p < 0.05$). Among 13 patients having reoperation, reoperation in 12 was prompted by degeneration of one or more bioprosthetic valves. Six of the patients who underwent reoperation died in the hospital, and 4 others died between 2 and 8 years after operation. These results support the view that mechanical prostheses provide better long-term results for triple-valve replacement than those produced using bioprostheses, primarily by reducing need for reoperation and its attendant complications.

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Results of triple cardiac valve replacement have been reported by many groups of investigators [1-9]. Few reports, however, have compared late results of simultaneous aortic, mitral, and tricuspid valve replacement at the same institution using different types of substitute valves [8, 9]. The purpose of this study was to determine if various combinations of mechanical and bioprosthetic valves influenced late morbidity and mortality in patients undergoing triple-valve replacement. This report describes such results in 40 hospital survivors of triple cardiac valve replacement at the National Heart, Lung and Blood Institute (NHLBI) over a 25-year period.

Material and Methods

A total of 63 patients underwent simultaneous aortic, mitral, and tricuspid valve replacement at the NHLBI from 1966 to 1990. Twenty-three patients were excluded from this analysis of late results. Twenty died within 30

days of operation or during initial hospitalization, and 3 patients who were referred from Iran, Romania, and Greece returned to their countries of origin immediately after operation and could not be followed up.

The remaining 40 patients were separated into four groups based on the types of substitute valves inserted. Five patients received mechanical prostheses in the aortic, mitral, and tricuspid positions, 5 received mechanical prostheses in the aortic and mitral positions and a bioprosthesis in the tricuspid position, 17 received a mechanical prosthesis in the aortic position and bioprostheses in the mitral and tricuspid positions, and 13 received 3 bioprostheses (Table 1). Although different valve combinations were placed over different time periods, it is expected that advances in myocardial protection and surgical technique would have a greater influence on short-term as opposed to long-term survival.

The 23 excluded patients had the following valves implanted: mechanical prostheses in 3, two mechanical prostheses and one bioprosthesis in 3, one mechanical prosthesis and two bioprostheses in 7, and three bioprostheses in 10. There were no significant differences between the patients who were excluded and the remaining 40 patients in terms of the types of valves or combinations of valves inserted.

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Table 1. The Four Groups

Group	Substitute Values			Total No. of Patients	Dates of Operation	Types of Substitute Valves Inserted				No. of Patients With Previous Valve Operation	No. of Previous Valve Operations	Type of Previous Operation				
	AV	MV	TV			AV	MV	TV	No.			MC	MVR	MVR	TVR	AVR
1	MP	MP	MP	5	1966-1971	SE	SE	SE	1	0	0	0	0	0	0	0
						SE	SE	BS	1							
						SE	SE	KS	1							
						SE	KS	KS	2							
2	MP	MP	BP	5	1980-1987	SE	SE	H	1	3	3	1	1	1	0	0
						BS	BS	H	1							
						SJM	SJM	H	3							
3	MP	BP	BP	17	1973-1982	SE	H	H	3	7	9	6	1	2	0	0
						BS	H	H	14							
4	BP	BP	BP	13	1970-1987	H	H	H	13	8	12	5	0	4	1	2
Total/mean				40						18	24	12	2	7	1	2

AV = aortic valve; AVR = aortic valve replacement; BP = bioprosthesis; BS = Björk-Shiley; H = Hancock; KS = Kay-Shiley; MC = mitral commissurotomy; MP = mechanical prosthesis; MV = mitral valve; MVR = mitral valve replacement; SE = Starr-Edwards; SJM = St. Jude Medical; TV = tricuspid valve; TVR = tricuspid valve replacement.

The end of the study was January 1, 1990, and all patients who were still alive were contacted within 2 months of this date. Follow-up was achieved primarily by yearly outpatient clinic visits, the records of which were reviewed. The duration of follow-up per patient ranged from 0.2 to 19.5 years (mean, 8.3 years), with a total of 331 years for 40 patients (100% complete). The ages of the 40 patients ranged from 27 to 69 years at operation (mean, 49 years); 73% were women. Eighteen of the patients had undergone a previous cardiac valve operation and 90% were in atrial fibrillation. A history of acute rheumatic fever was reported by 28 patients. No patient had active infective endocarditis at operation.

The population of patients of the Surgery Branch of the NHLBI was unique in that there was accurate ongoing follow-up of all patients in the outpatient clinic every 1 to 2 years for life. All underwent complete preoperative evaluation, and 38 of the 40 patients had a postoperative cardiac catheterization at less than 9 months during a rehospitalization for extensive studies. A physical examination, electrocardiogram, chest radiograph, and echocardiogram were obtained at each clinic visit. Any patient with a change in symptom complex or new echocardiographic findings underwent cardiac catheterization. If a clinic appointment was missed, the patient and the private physician were contacted to find out the status of the patient. Outside cardiac catheterization results were entered into the database, as were the cause of death or autopsy results.

Morbidity and mortality results for each group were expressed in both linearized (percent/patient year) and actuarial terms. Preoperative and postoperative data between groups were compared using unpaired Student's *t* tests, and data within the same group were compared using paired Student's *t* tests. Kaplan-Meier actuarial data were compared by the Mantel-Haenszel test. Total mortality as expressed in Table 3 included all deaths during

the follow-up period. However, in the actuarial survival analysis, the patients who underwent reoperation or who died of noncardiac causes were withdrawn from further analysis on that particular date and were not treated as having died. The actuarial analysis of complications (thromboembolism, anticoagulant-related hemorrhage, and reoperation) included only first events, fatal or non-fatal. Thromboembolism was defined as any new postoperative neurological or systemic ischemic deficit, whether central or peripheral, temporary or permanent. Patients on anticoagulant or antiplatelet agents with episodes of hemorrhage causing death, stroke, hospitalization, transfusion, or operation were classified as having anticoagulant-related hemorrhage [10]. Those patients taking warfarin, but with subtherapeutic prothrombin times at the time of a morbid event, were classified as having a thromboembolism rather than anticoagulant-related hemorrhage. In the patients receiving warfarin, a prothrombin time of 1.5 to 2 times normal was recommended.

Valve-related morbidity and mortality included all late deaths, reoperations, thromboembolism, and anticoagulant-related hemorrhage but excluded patients who died in end-stage congestive heart failure with normally functioning prosthetic valves or documented noncardiac deaths. Note that this is a measure of valve-related late morbidity and mortality and specifically excludes 30-day and in-hospital mortality, which was 31%.

Two of the 23 excluded patients had a thromboembolic event at less than 30 days (both with two mechanical prostheses and one bioprosthesis combination); both events were strokes, and the patients eventually died of pneumonia and coma. The other deaths in this group were caused by low cardiac output syndrome (6), coagulopathy (3), myocardial infarction (2), multisystem organ failure (2), sepsis (1), pneumonia (1), diverticulitis (1), perforated ulcer (1), and arrhythmia (1).

Table 2. Preoperative Data

Group	Substitute Valves			Hospital Survivors	Mean Age (y)	Sex (M/F)	History of:			Mean FC	Mean PA (s/d; mm Hg)	Mean CI ($L \cdot \min^{-1} \cdot m^{-2}$)	Type of Native Valve Lesion					
	AV	MV	TV				ARF	IE	AF				MS AS	MS AS	MS AR	MS AR	MR AS	MR AR
													TS	TR	TS	TR	TR	TR
1	MP	MP	MP	5	44	1/4	3	1	5	3.4	58/33	2.4	2	2	1	0	0	0
2	MP	MP	BP	5	54	0/5	3	0	5	2.8	67/26	1.9	1	2	2	0	0	0
3	MP	BP	BP	17	46	5/12	14	0	14	3.3	53/26	1.9	8	5	1	2	1	0
4	BP	BP	BP	13	52	5/8	8	1	12	3.3	62/31	2.0	1	4	3	2	1	2
Total/mean				40	49	11/29	28	2	36	3.3	59/27	2.0	12	13	7	4	2	2

AF = atrial fibrillation; AR = aortic regurgitation; ARF = acute rheumatic fever; AS = aortic stenosis (with or without regurgitation); AV = aortic valve; BP = bioprosthesis; CI = cardiac index; F = female; FC = functional class (New York Heart Association); IE = infective endocarditis; M = male; MP = mechanical prosthesis; MR = mitral regurgitation; MS = mitral stenosis (with or without regurgitation); PA = pulmonary artery pressure; s/d = peak systole/end-diastole; TR = tricuspid regurgitation; TS = tricuspid stenosis (with or without regurgitation); TV = tricuspid valve.

Results

No significant differences among the four groups of patients were found in age at operation, frequency of history of rheumatic or infective endocarditis, atrial fibrillation, mean functional class, pulmonary arterial pressure, or cardiac index. All 40 patients underwent cardiac catheterization before operation (<9 months). The mean postoperative functional class improved significantly from 3.3 to 1.6 ($p < 0.05$). Thirty-five of the 40 patients underwent cardiac catheterization postoperatively. The mean pulmonary arterial systolic/diastolic pressures decreased from 59/27 to 40/17 mm Hg ($p < 0.05$), and the mean cardiac index increased from 2.0 to $2.6 L \cdot \min^{-1} \cdot m^{-2}$ ($p < 0.05$) (Tables 2, 3). Twenty-nine of the 40 patients took warfarin, including all 27 patients who had a mechanical prosthesis and 2 of the 13 patients who had three bioprostheses because of atrial fibrillation.

Survival

The actuarial survival of the 40 hospital survivors was 78%, 74%, and 44% at 5, 10, and 15 years (Fig 1). The differences among the four groups were not significant at any of these three intervals (Fig 2). The mortality expressed in linear terms ranged from 4.0 to 7.7%/year.

Twenty-one patients died during the follow-up period: 6 patients of chronic congestive heart failure, 1 of intracerebral hemorrhage while taking warfarin, 1 of cancer, and 3 of natural causes. Ten patients died after reoperation to replace one or more of the substitute valves, of whom 6 died before hospital discharge and 4 died late after reoperation (2 to 8 years).

Reoperation

Actuarial freedom from reoperation at 5 and 10 years was 96% and 54% (see Fig 1). The rate of reoperation in groups with three bioprostheses or with one mechanical prosthesis and two bioprostheses was significantly higher ($p < 0.05$) than that in the groups with three mechanical prostheses or two mechanical prostheses and one bioprosthesis at 10 and 15 years (Fig 3). Rereplacement was required in 13 (33%) of the 40 patients, a frequency of 3.9%/year (Table 4). The mean interval from triple-valve replacement to reoperation was 8.4 years. No patient in the group with three mechanical prostheses or the group with two mechanical prostheses and one bioprosthesis required reoperation. Nine (53%) of the 17 patients in the group with one mechanical prosthesis and two bioprostheses underwent reoperation. The mitral bioprosthesis

Table 3. Postoperative Data

Group	Substitute Valves			Hospital Survivors	Total Years FU ^a	Mean Years FU/pt	Mean FC	Mean PA (s/d; mm Hg)	Mean CI ($L \cdot \min^{-1} \cdot m^{-2}$)	Warfarin Therapy	Total Mortality (%/y)	TE (%/y)	ARH (%/y)	Re-operation (%/y)
	AV	MV	TV											
1	MP	MP	MP	5	39	7.9	1.7	40/18	2.6	5	3 (7.7)	2 (5.1)	0	0
2	MP	MP	BP	5	23	4.6	1.8	43/19	2.9	5	1 (4.3)	0	1 (4.3)	0
3	MP	BP	BP	17	168	9.9	1.5	37/16	2.5	17	13 (7.7)	9 (5.4)	5 (3.0)	9 (5.4)
4	BP	BP	BP	13	101	7.8	1.7	42/17	2.7	2	4 (4.0)	0	0	4 (4.0)
Total/mean				40	331	8.3	1.6	40/17	2.6	29 (73%)	21 (6.3)	11 (3.3)	6 (1.8)	13 (3.9)

^a Actual follow-up was 100% of potential follow-up.

ARH = anticoagulant-related hemorrhage; AV = aortic valve; BP = bioprosthesis; CI = cardiac index; FC = functional class (New York Heart Association); FU = follow-up; MP = mechanical prosthesis; MV = mitral valve; PA = pulmonary artery pressure; pt = patient; s/d = peak systole/end-diastole; TE = thromboembolism; TV = tricuspid valve.

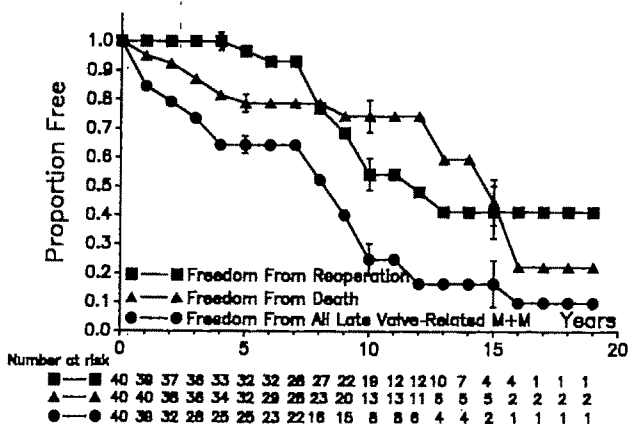


Fig 1. Actuarial curves of freedom from reoperation, death, and all valve-related late morbidity and mortality (M + M) in 40 hospital survivors of combined aortic, mitral, and tricuspid valve replacement. Patients who required reoperation were censored at the time of reoperation on the survival analysis.

was replaced in 8 of these patients, all of whom had bioprosthetic structural deterioration, and in 1 patient who had isolated replacement of a mechanical aortic prosthesis because of recurrent thromboembolic events (see Table 4, patient 1). Four of the 13 patients in the group with three bioprostheses underwent reoperation, with the mitral bioprosthesis being replaced in each patient. All 13 patients who underwent reoperation had a bioprosthesis in the tricuspid and mitral positions; replacement of the bioprosthesis in the tricuspid position was carried out in 9 patients, although prosthetic tricuspid valve disease was not the primary reason for reoperation. The in-hospital mortality for reoperation after triple cardiac valve replacement was 46% (6/13 patients), with an additional 4 patients dying 2 to 8 years after reoperation.

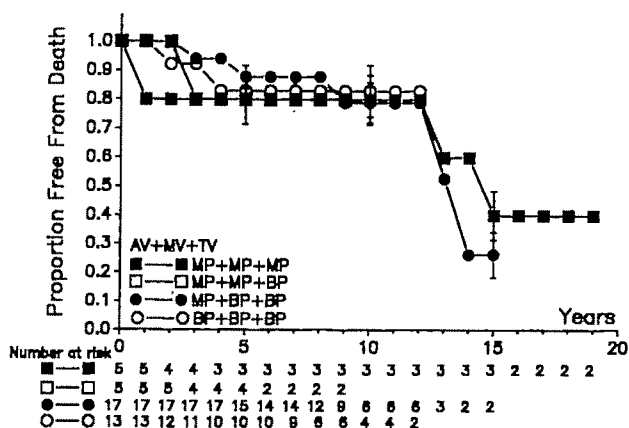


Fig 2. Comparison of actuarial curves of freedom from death in 40 hospital survivors of combined aortic, mitral, and tricuspid valve replacement with four different combinations of substitute valves. Patients who required reoperation were censored at the time of reoperation. (AV = aortic valve; BP = bioprosthesis; MP = mechanical prosthesis; MV = mitral valve; TV = tricuspid valve.)

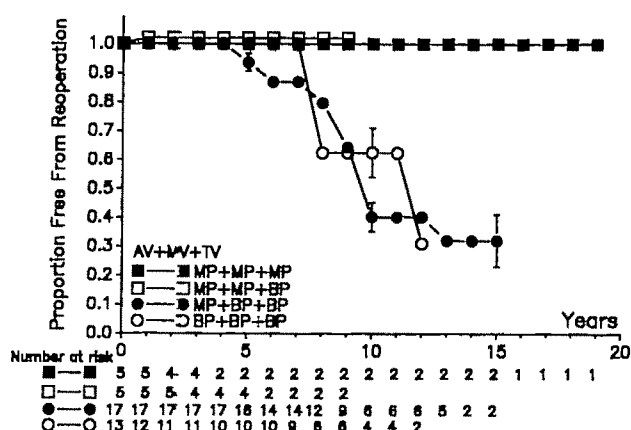


Fig 3. Comparison of actuarial curves of freedom from reoperation in 40 hospital survivors of combined aortic, mitral, and tricuspid valve replacement with four different combinations of substitute valves. (AV = aortic valve; BP = bioprosthesis; MP = mechanical prosthesis; MV = mitral valve; TV = tricuspid valve.)

Thromboembolism and Anticoagulant-Related Hemorrhage

Freedom from combined thromboembolism and anticoagulant-related hemorrhage, expressed in actuarial terms, was 68% and 56% at 5 and 10 years for all 40 patients (Figs 4, 5). Thromboembolism occurred in 11 of the 40 patients (3.3%/year). Seventy-five of the patients who presented for postoperative cardiac catheterization were in atrial fibrillation. Eight of 11 patients with thromboembolism were in and out of atrial fibrillation at the time of their event. These events occurred only in patients who had a mechanical prosthesis, and only one of these events was fatal (Fig 6). Anticoagulant-related hemorrhage occurred in 6 of the 40 patients. No patient in the group with three bioprostheses had this complication, and no event was fatal (Fig 7). Four of 6 patients were in atrial fibrillation at the time of hemorrhage. Patients with one or more mechanical prostheses had significantly higher rates of these complications than did those patients without a mechanical prosthesis ($p < 0.05$) (see Fig 5). The one mechanical prosthesis/two bioprostheses combination had the highest occurrence of thromboembolism, and 14 of 17 patients in this group had a Björk-Shiley mechanical aortic prosthesis.

Freedom from all valve-related morbidity and mortality was 65%, 25%, and 20% at 5, 10, and 15 years (see Fig 1). The group of patients with two or more mechanical prostheses had a lower freedom from all late valve-related morbidity and mortality at 10 years than did the group with two or more bioprostheses (Fig 8). Also not reflected in Figure 8 is the fact that reoperation in the groups with two or more bioprostheses was associated with considerable mortality.

Comment

Analysis of results of triple-valve replacement is more complex than that of single- or double-valve replacement. The same patient may have different types of substitute

Table 4. Clinical Findings in 13 Patients Who Underwent Reoperation After Initial Triple Cardiac Valve Replacement

Patient No.	Age at Reop (y)	Sex	Reop at NIH	Initial Substitute Valves			Interval 1st to 2nd Operation (y)	Type of Reoperation (substitute valve)			Hospital Death
				AV	MV	TV		AVR	MVR	TVR	
1	66	F	+	MP	BP	BP	4.2	BP	0	0	0
2	38	M	+	MP	BP	BP	5.0	MP	MP	0	+
3	52	M	+	MP	BP	BP	7.5	0	BP	BP	0
4	44	M	+	MP	BP	BP	8.1	0	BP	BP	+
5	57	F	0	MP	BP	BP	8.3	0	BP	0	0
6	45	M	+	MP	BP	BP	9.0	0	MP	BP	+
7	55	M	+	MP	BP	BP	9.6	BP	BP	0	+
8	45	F	+	MP	BP	BP	9.9	0	MP	BP	0
9	62	F	+	MP	BP	BP	12.3	0	BP	BP	0
10	39	F	0	BP	BP	BP	7.8	0	BP	BP	0
11	60	M	+	BP	BP	BP	7.8	MP	MP	BP	0
12	62	F	+	BP	BP	BP	7.9	MP	MP	MP	+
13	55	F	+	BP	BP	BP	11.3	0	MP	MP	+
Total/Mean	52	7F, 6M	8				8.4	5	12	9	6

AV = aortic valve; AVR = aortic valve replacement; BP = bioprosthesis; F = female; M = male; MP = mechanical prosthesis; MV = mitral valve; MVR = mitral valve replacement; NIH = National Institutes of Health; Reop = reoperation; TV = tricuspid valve; TVR = tricuspid valve replacement.

valves inserted, and different patients may have many combinations of the same valves. Because triple-valve replacement is an infrequently performed operation, acquisition of sufficient data for meaningful analysis requires long intervals during which procedures, surgeons, valve preferences, and availability of valve types change. The patient population in the present study was seen during a 25-year period, with 6 different surgeons performing triple-valve replacement in the 63 described patients.

In the present study, the number of patients having a mechanical prosthesis in all three valve positions was too small to make meaningful comparison with the group with a bioprosthesis in all positions. However comparison of the 10 patients with two or more mechanical prostheses

with the 30 patients with two or more bioprostheses indicated no significant differences in frequency of thromboembolic events (2/10 versus 9/30), anticoagulant-related bleeding (1/10 versus 5/30), or late death (4/10 versus 17/30). The late death rate changes to 1 of 10 and 3 of 30 when the deaths due to end-stage congestive heart failure and after reoperation are censored. Reoperation in 12 of the 13 patients was prompted by degeneration of one or more bioprostheses. Twelve of the 30 bioprostheses in the mitral position and nine of the 35 bioprostheses in the tricuspid valve position were replaced. No patient with a mechanical prosthesis in both left-sided valve positions had reoperation.

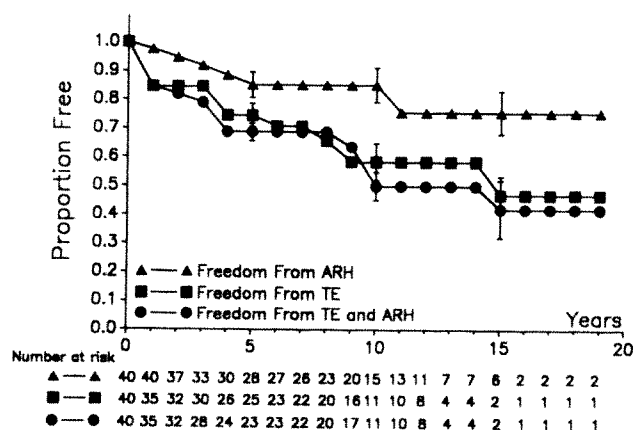


Fig 4. Actuarial curves of freedom from thromboembolism (TE), anticoagulant-related hemorrhage (ARH), and combined TE and ARH in 40 hospital survivors of combined aortic, mitral, and tricuspid valve replacement.

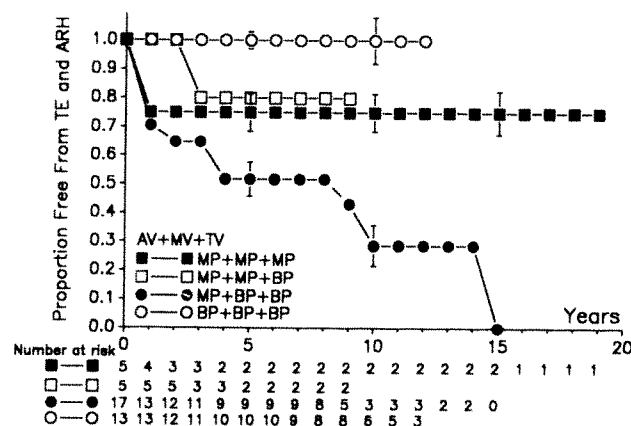


Fig 5. Comparison of actuarial curves of freedom from combined thromboembolism (TE) and anticoagulant-related hemorrhage (ARH) in 40 hospital survivors of combined aortic, mitral, and tricuspid valve replacement with four different combinations of substitute valves. (AV = aortic valve; BP = bioprosthesis; MP = mechanical prosthesis; MV = mitral valve; TV = tricuspid valve.)

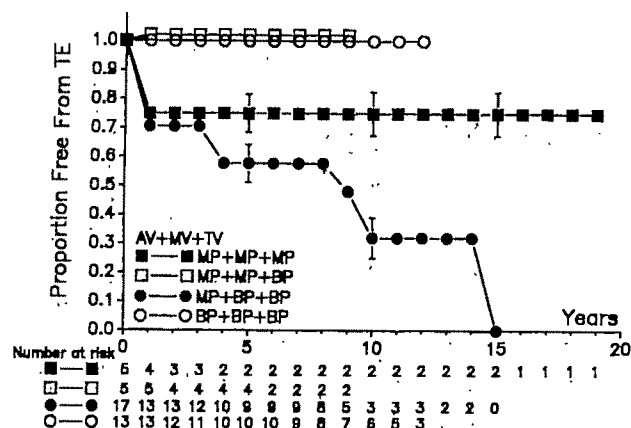


Fig 6. Comparison of actuarial curves of freedom from thromboembolism (TE) in 40 hospital survivors of combined aortic, mitral, and tricuspid valve replacement with four different combinations of substitute valves. (AV = aortic valve; BP = bioprosthesis; MP = mechanical prosthesis; MV = mitral valve; TV = tricuspid valve).

Neither the early nor late results of triple-valve replacement described above are ideal. Of 63 patients initially having triple-valve replacement, 31% died in the early postoperative period, and of the remaining 40 patients, 52% died later. Nevertheless, the New York Heart Association functional class improved by 1 class or more in 90% of patients, with 45% becoming class I (asymptomatic). Patients with a bioprosthesis in one or both left-sided valve positions had a significantly higher reoperation rate compared with those in whom both left-sided cardiac valves were replaced with a mechanical prosthesis. Thus, these data provide evidence that use of bioprostheses for triple-valve replacement is not ideal.

Other factors also provide evidence that bioprostheses should be avoided, at least for replacement of the mitral and aortic valves and probably also for the tricuspid valve. In the present study, 45% of the 40 patients had one (12

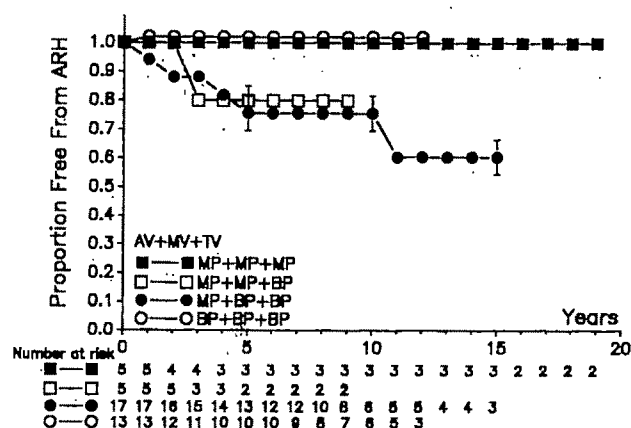


Fig 7. Comparison of actuarial curves of freedom from anticoagulant-related hemorrhage (ARH) in 40 hospital survivors of combined aortic, mitral, and tricuspid valve replacement with four different combinations of substitute valves. (AV = aortic valve; BP = bioprosthesis; MP = mechanical prosthesis; MV = mitral valve; TV = tricuspid valve.)

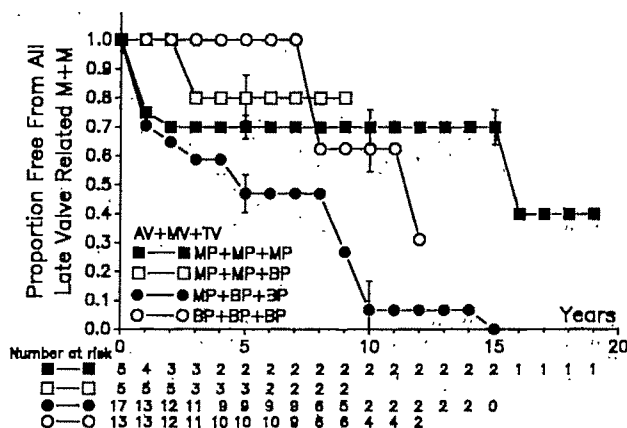


Fig 8. Comparison of actuarial curves for freedom from all valve-related mortality and morbidity (M + M: death, reoperation, thromboembolism, and anticoagulant-related hemorrhage) in 40 hospital survivors of combined aortic, mitral, and tricuspid valve replacement with four different combinations of substitute valves. (AV = aortic valve; BP = bioprosthesis; MP = mechanical prosthesis; MV = mitral valve; TV = tricuspid valve.)

patients) or two (6 patients) cardiac operations before the triple-valve replacement. All of these 18 patients were among the 35 in whom one or more bioprostheses were inserted at triple-valve replacement. It is well established from numerous studies in the last 20 years that a porcine bioprosthesis in any valve position will degenerate if the patient survives a sufficiently long time [9, 11-13]. Five patients who later had reoperation after triple-valve replacement had already undergone one or more valve operations before triple-valve replacement. Thus, reoperation in 3 patients represented their fourth cardiac valve operation, and 2 of them died early postoperatively.

Reported experience with use of a mechanical prosthesis for tricuspid valve replacement has not been encouraging [14-17]. Most reports, however, have provided results using a mechanical prosthesis that today is either never used or rarely used for tricuspid valve replacement. Only 5 of our 40 patients had the tricuspid valve replaced with a mechanical prosthesis: Starr-Edwards in 1, Kay-Shiley in 3, and Björk-Shiley in 1. These three types of mechanical prostheses are rarely used today for tricuspid valve replacement. In contrast, early results of replacement of the tricuspid valve with a St. Jude Medical valve are encouraging [18, 19].

Any study reporting results of tricuspid valve replacement can legitimately ask whether its replacement was necessary in the first place [20-24]. It is relatively easy to justify tricuspid valve replacement in a patient with severe rheumatic tricuspid stenosis, as was the situation in 18 (45%) of our 40 patients. Disagreement on the need for tricuspid valve replacement centers on the purely regurgitant tricuspid valve (no element of stenosis), which was present in 22 (55%) of our patients. When the right ventricular systolic pressure is less than 40 mm Hg, the purely regurgitant tricuspid valve is usually anatomically abnormal. Such hemodynamics were present in 2 of our 40 patients. Thus, 20 of our 40 patients had pure tricuspid

regurgitation with elevated right ventricular systolic pressure. Most, if not all, of these patients would probably undergo tricuspid valve annuloplasty today rather than tricuspid valve replacement [21-23].

Data from this analysis support the view that patients having triple-valve replacement have fewer total complications and greater longevity when both left-sided valves are replaced with a mechanical prosthesis. The evidence is not yet available to show that a low-profile, ventral flow mechanical prosthesis, such as the St. Jude Medical, provides better outcome than does a bioprosthesis when used in the tricuspid position. It would seem most advantageous, however, if all three valves could be mechanical ones, the advantage being that valve degeneration (and therefore reoperation) would be far less likely. Combining mechanical and bioprosthetic valves in the same patient, especially if the patient already has to be anticoagulated, imparts the disadvantages of both valve types and the advantages of neither.

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Bilateral Intralobar Pulmonary Sequestration With Horseshoe Lung

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We present an unusual case of a young woman with a several-month history of bronchopulmonary infection, symptomatic on the left side, who underwent complete studies showing bilateral pulmonary sequestration with suspected bridging tunnel. A bilateral resection was performed as a single procedure through a left thoracotomy.

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Itralobar pulmonary sequestration is a segment of pulmonary parenchyma not connected to the tracheo-bronchial tree, within the normal pleural investment, receiving arterial supply from the systemic circulation and venous return usually through pulmonary veins and rarely through systemic venous drainage [1]. This lesion, whether congenital or acquired [1], occurs mainly in the basal segments of the lower lobes and is more frequently unilateral than bilateral. In 400 reported cases of intralobar sequestration, Savic and associates [2] found only 2 cases of bilateral intralobar sequestration.

The horseshoe lung [3, 4] is a very rare congenital malformation in which the basal segments of both lower lobes are fused by an isthmus of pulmonary tissue behind the heart. It may be associated with the scimitar syndrome, in which the leading feature is an anomalous drainage of some or all of the pulmonary veins of the right lung which, in turn, may be associated with other congenital malformations.

A 20-year-old woman with a 7-month history of recurrent bronchopulmonary infection was not responding to medical treatment and continued to have productive cough, fever, and weight loss. She was symptomatic on the left side only. A chest roentgenogram showed pulmonary density and infiltrate involving the basal segments of the left lower lobe. Computed tomographic scan of the chest showed bilateral pulmonary lesions on the left and right lower lobes (consistent with bilateral intralobar sequestration), more prominent on the left side, with a possible bridging tunnel but no clear evidence of abnormal vessels (Fig 1). The angiogram revealed arterial supply from the abdominal aorta to the left sequestered segment and from the thoracic aorta, which bifurcated, to the right and left lower lobe sequestrations. Venous drainage was into the

inferior pulmonary vein on the left side, but not clearly demonstrated on the right side (Fig 2).

The plan was to resect the symptomatic sequestration on the left side and then to consider resection of the lesion on the right side.

A left thoracotomy was performed. A lobectomy was decided on because an irregular mass was found occupying the basal segments of the lower lobe, with severe collateral inflammatory infiltration around it and extending into the superior segment. Three small arteries coming through the diaphragm were divided. The inferior pulmonary ligament and adjacent portion of the lower lobe were fixed to the mediastinum by what, on dissection, proved to be the connecting tunnel with a central orifice. Purulent secretion was draining from the right and left sides of this orifice. The tunnel measured 3 cm in diameter and extended behind the heart, entering the right pleural cavity and reaching the basal segments of the right lower lobe, where a well-demarcated area of about 3 × 6 cm was the right lower lobe sequestration. This portion of the right lower lobe and the connecting tunnel were brought into the left pleural cavity, and a wedge resection of the sequestered area was done (Fig 3). It is important to mention that during the dissection of the mediastinum and before the right pleural cavity was entered, two small arteries were found, one going toward the left and the other toward the right sequestered segments; these arteries were divided. No venous return was identified on the right side. A left lower lobe lobectomy was completed.

The patient recovered very well, with excellent clinical improvement, and returned to normal life. The pathological report showed bilateral pulmonary sequestration with acute and chronic infection and cavitory lesions on both sides. The connecting tunnel was composed of a central bronchus surrounded by pulmonary tissue and was covered by pleura; it also showed inflammatory changes. Computed tomographic scan 5 months later proved no residual pathological findings.

Comment

Bilateral pulmonary sequestration is a rare abnormality. Only 6 well-documented cases have been reported [5]. One was found in the autopsy of an infant. Two other patients had a resection of the symptomatic side only. The other 3 cases [5-7], only 1 of which had bilateral symptoms [6], were resected by staged bilateral thoracotomies. The pathology reports of these 3 cases were consistent with intralobar pulmonary sequestration.

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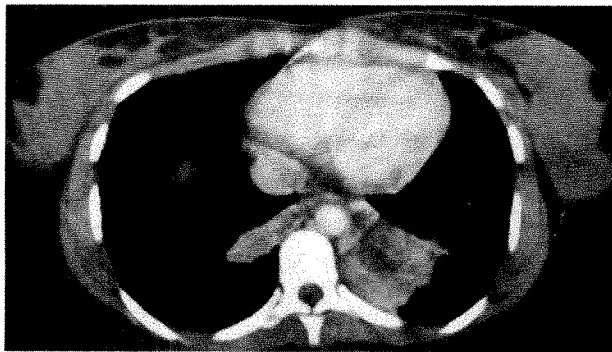


Fig 1. Computed tomographic scan of chest with bilateral pulmonary lesions consistent with bilateral pulmonary sequestration and possible bridging tunnel.

The most common cause of morbidity in intralobar sequestration is infection resulting from the air passage that may develop between the normal lung parenchyma and the sequestered area. All authors mentioned agree that even asymptomatic sequestration should be resected to prevent infection. Once infection occurs, a major resec-

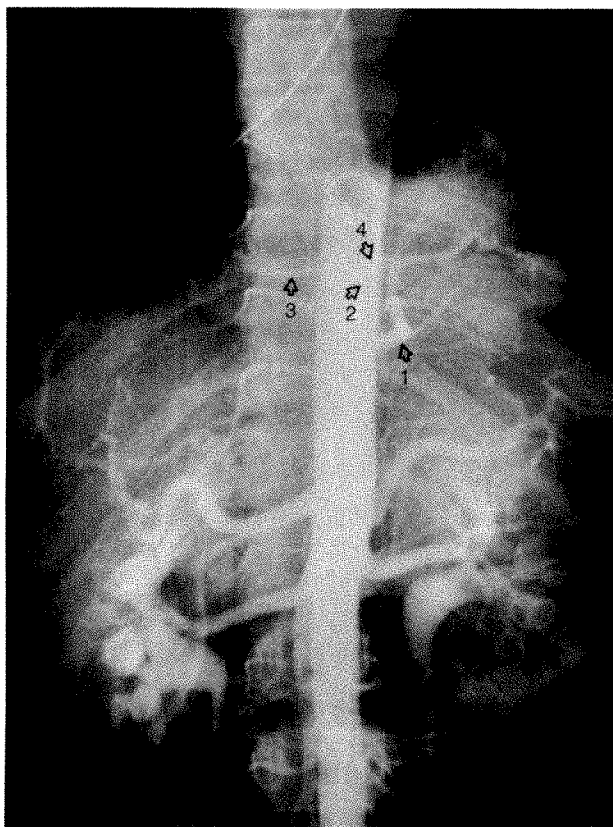


Fig 2. Angiogram demonstrating arterial supply from abdominal aorta to left sequestered segment (1), and from thoracic aorta (2) to the right sequestered segment (3) as well as the left sequestered segment (4).

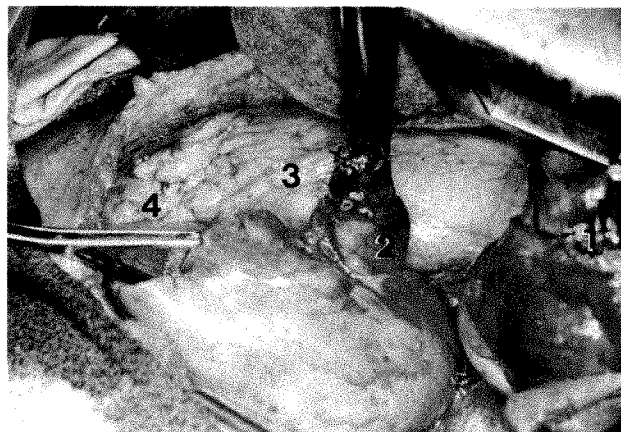


Fig 3. Origin of connecting tunnel on left lower lobe (1). Connecting tunnel and sequestered segment (2) on right lower lobe were brought behind the heart (3) and through the mediastinum (4) into the left pleural cavity.

tion such as a lobectomy may be necessary, instead of a lesser resection such as a segmentectomy or wedge resection. Other causes of morbidity are massive bleeding [7] and the occurrence of tumors in the sequestered area [8].

Finally, our case clearly supports the advice of Roe and associates [7] and Juettner and colleagues [5] that staged bilateral thoracotomies are the approach indicated for the treatment of bilateral pulmonary sequestration. Median sternotomy would not have enabled us to resect the connecting tunnel.

We gratefully acknowledge the collaboration of Dr Jacob Groopman of the Pulmonary Department and Dr David Bryk of the Radiology Department at Maimonides Medical Center.

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Giant Hamartoma of the Lung With a High Production of Carbohydrate Antigen 19-9

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A rare case of a giant pulmonary hamartoma with a high production of carbohydrate antigen (CA) 19-9 is presented. A 43-year-old woman with complaints of cough, fever, and chest pain was diagnosed as having a posterior mediastinal tumor with pneumonia. The serum CA 19-9 level was high. A thoracotomy revealed an intrapulmonary solid mass with a histologic diagnosis of cartilagi-

nous hamartoma with no evidence of malignancy. The CA 19-9 concentration in the mucus of the tumor was high, and postoperatively the serum CA 19-9 level returned to normal. The CA 19-9 could be immunohistochemically demonstrated on the surface of the tumor.

(*Ann Thorac Surg* 1993;55:511-3)

Carbohydrate antigen (CA) 19-9 is an antigen that was originally found on the surface of colon cancer cells detected by murine monoclonal antibody [1]. It is a clinically well-known tumor marker for diagnosis of gas-

trointestinal and pancreatic malignancies. Recently there have been some reports on elevation of CA 19-9 level in nonmalignant respiratory diseases [2, 3], such as bronchogenic cyst, intralobar sequestration, idiopathic pulmonary

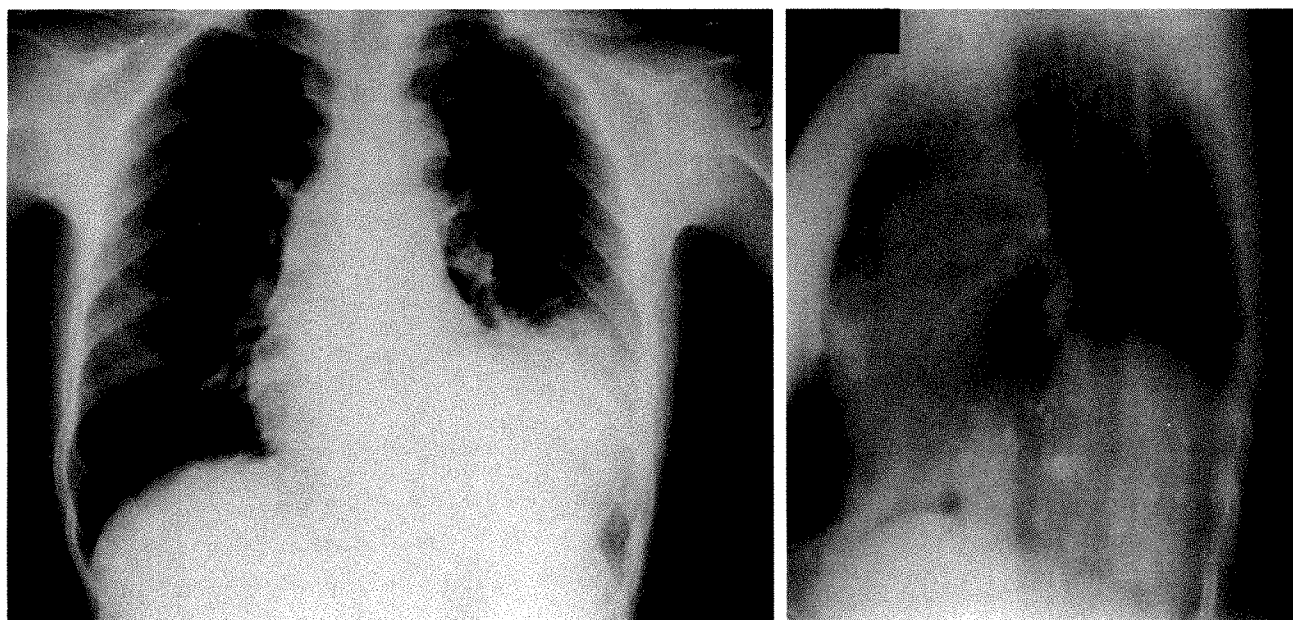
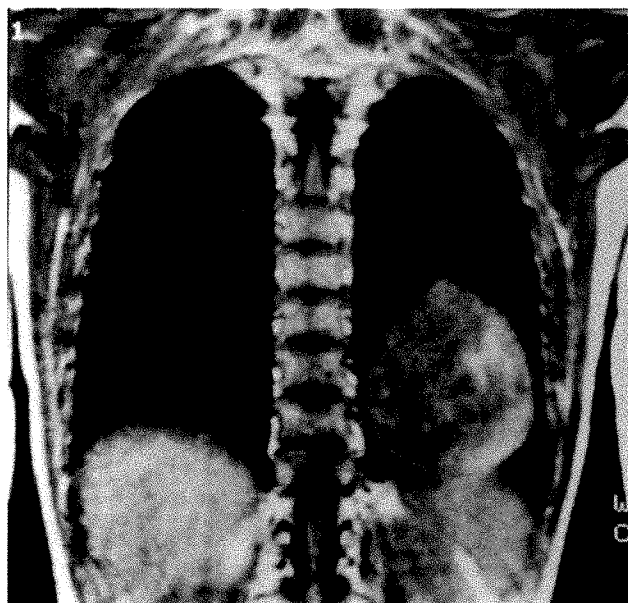


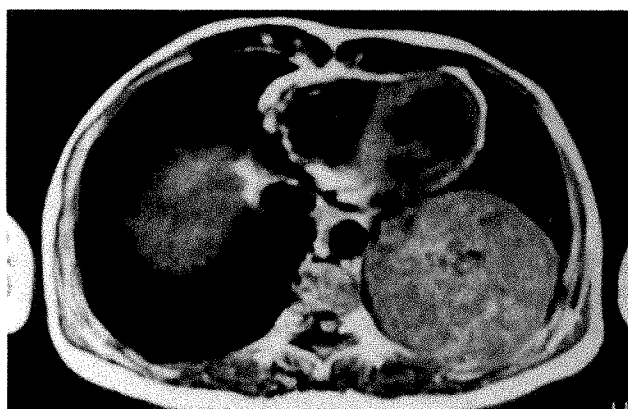
Fig 1. (A) Chest roentgenogram showing an abnormal mass shadow at the left lower lung field with an infiltration around it. (B) Lateral view of tomography at the same time showing a large well-margined mass with scattered mottled calcification.

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A



B

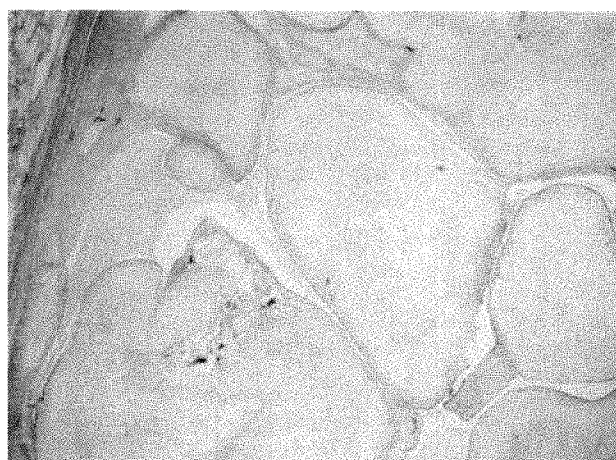
Fig 2. Nuclear magnetic resonance imaging of the chest revealing a 9-cm well-defined huge tumor, which seems to have no lung tissue between it and the posterior chest wall, with scattered high signal lesions in it.

fibrosis, and bronchial asthma. Here we report a case of giant hamartoma of the lung with a high level of CA 19-9 in both the serum and the secreted mucus.

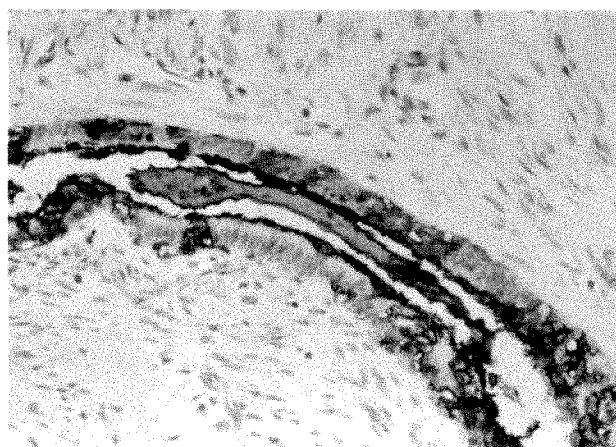
A 43-year-old woman, who visited a private physician with complaints of productive cough, fever, and left chest pain, underwent a chest roentgenogram, which revealed an abnormal mass shadow in her left lung. She was referred to our hospital for further evaluation. Chest roentgenograms showed a large tumor with an infiltration in the left lower lung field (Fig 1). A physical examination revealed no abnormalities but diminished breath sounds over the left lower lobe. Laboratory tests revealed mild leukocytosis ($10.6 \times 10^9/L$ [$10,600/\mu L$]) and an elevated level of C-reactive protein ($>6+$). The serum CA 19-9 level was 460.0 U/mL (normal, <37.0 U/mL), the Sialyl Lewis X-i level was 66.4 U/mL (normal, <38.0 U/mL) but levels

of carcinoembryonic antigen and α -fetoprotein were within normal range. Administration of cephalosporin resulted in an improvement of the symptoms and in a decrease in the serum CA 19-9 and Sialyl Lewis X-i levels (126.3 and 37.7 U/mL, respectively). Nuclear magnetic resonance imaging of the chest demonstrated a large tumor with a well-defined margin (Fig 2). The presumptive diagnosis was a posterior mediastinal teratoma or a neurogenic tumor.

A thoracotomy revealed the tumor to be an intrapulmonary solid mass, and a left lower lobectomy was performed. The resected tumor ($9 \times 9 \times 8.7$ cm) was gyrus-shaped and cartilaginously hard, and weighed 576 g (without the lung tissue) with some viscous fluid in it. The CA 19-9 concentration in the mucus was 532,960 U/mL. Histologic examination showed chondromatous hamartoma with no evidence of malignancy. To see which



A



B

Fig 3. (A) Histologic examination revealing that this tumor is made of cartilage and epithelium without any malignant component. Pathologic diagnosis was chondromatous hamartoma. (Hematoxylin and eosin, $\times 20$ before 50% reduction.) (B) Immunoperoxidase staining with anti-CA 19-9 monoclonal antibody. The columnar epithelial cells lining the mesenchymal tissue give a positive reaction for CA 19-9. ($\times 200$ before 50% reduction.)

component of the tumor produced CA 19-9, we examined the localization of CA 19-9 immunohistochemically by the avidin-biotin-peroxidase complex method [4]. The CA 19-9 was demonstrated in some epithelial cells of the hamartoma (Fig 3). The postoperative course was uneventful, and the patient's serum CA 19-9 level returned quickly to the normal range. She has been in good health since this episode, with a normal serum CA 19-9 level.

Comment

Hamartoma is a common benign pulmonary tumor that generally occurs in adults. Most hamartomas are asymptomatic and are found at the peripheral lung parenchyma. Many resected hamartomas are around 2.5 cm in diameter, and only 12 cases have been reported in Japan to be more than 6 cm. It is generally easy to make a diagnosis of hamartoma when typical mottled calcification scattered throughout a discrete, smooth-margined mass is seen with normal surrounding lung [5]. However, in some cases it is quite difficult to distinguish hamartomas from pulmonary malignancies. Although the present case had almost all the radiographic characteristics, we never suspected a hamartoma because there was no room for normal lung tissue between lung and chest wall by computed tomography and nuclear magnetic resonance imaging, and because the serum CA 19-9 level was high.

Carbohydrate antigen 19-9 is a common tumor marker that is mainly present in gastrointestinal or pancreatic malignancies. A small amount of CA 19-9 is also present in normal cells, such as those of pancreatic duct, biliary duct, salivary gland ducts, and prostate and bronchial glands. It is certain that the hamartoma of this patient produces CA 19-9 because (1) no gastrointestinal or pancreatic problems were found perioperatively, (2) the serum CA 19-9 level returned to normal postoperatively, (3) mucus of the tumor contained a high concentration of CA 19-9, and (4) immunoperoxidase staining with anti-CA

19-9 monoclonal antibody could show strongly positive epithelial cells.

The term *hamartoma*, derived from the Greek words meaning "error" and "tumor," was proposed by Albrecht in 1904. Although originally it was thought to represent a malformation rather than a neoplastic disease, several investigators have suggested that the epithelial and the mesenchymal components, or the mesenchymal components alone, might be neoplastic [6, 7]. Recently Fletcher and associates [8] have demonstrated the neoplastic feature of the mesenchymal component, whereas epithelial cells appeared to be reactive, by an immunohistochemical/cytogenetic approach. In the present case, it is uncertain whether the lining epithelium rich in CA 19-9 production was neoplastic or reactive. Further research about CA 19-9 and pulmonary hamartoma may lead to resolution of this biphasic tumor.

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Coronary Revascularization in a Patient With Porcelain Aorta and Calcified Great Vessels

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Calcification of the aorta and great vessels in coronary artery bypass patients remains a challenging dilemma for the surgeon regarding bypass technique, choice of conduit, and available location of proximal anastomotic sites. Internal mammary artery flow may be inadequate, and the risk of systemic emboli from a diseased aorta is substantial. We report a case of a 69-year-old diabetic patient with a porcelain aorta extending into the aortic

arch and great vessels who was revascularized using an altered anastomotic technique of right coronary artery endarterectomy for proximal anastomosis of vein grafts. Intraoperative echocardiographic evaluation of the aorta and arch was beneficial in determining extent of calcification.

(*Ann Thorac Surg* 1993;55:514-5)

Extensive calcification of the ascending aorta, transverse arch, and the arch vessels is an infrequent but alarming finding during performance of coronary artery bypass grafting. The discovery of "porcelain aorta" requires technical changes in cardiopulmonary bypass as well as in revascularization techniques. Prior reports have discussed a "no-touch technique" using arterial conduits only and hypothermic fibrillatory arrest, use of arch vessels for proximal anastomoses, and even aortic endarterectomy in dealing with this problem [1, 2]. A technique that uses endarterectomy of the proximal right coronary artery (RCA) with vein graft insertion at this level is the subject of this report. Intraoperative echocardiography also proved extremely helpful in management of this difficult problem.

A 69-year-old diabetic woman with severe triple-vessel coronary artery disease underwent routine coronary revascularization. Intraoperative palpation of the aorta revealed severe calcification of the aorta, arch, and innominate origin. Intraoperative transesophageal and epicardial echocardiography was performed before cardiopulmonary bypass and demonstrated circumferential calcification of the ascending and descending aorta with extension well into the innominate artery (Fig 1).

The patient's femoral artery was cannulated, and she was placed on femoral-right atrial bypass and cooled to 22°C. Left ventricular venting was performed through the right superior pulmonary vein. During cooling the left internal mammary artery (IMA) was prepared and found to have adequate flow. The right IMA was not used because of its small size and the severe diabetic state of the patient. The greater saphenous vein provided adequate additional conduit. Under hypothermic fibrillatory

arrest the left IMA was anastomosed end-to-side to the left anterior descending artery. No sequential IMA anastomoses were done because of the diminutive size of the mammary artery. Distal saphenous vein anastomoses were performed to the posterior descending artery, mid-obtuse marginal artery, and a small diagonal branch of the left anterior descending artery. The proximal RCA was totally occluded, but palpation of its proximal portion revealed it to be soft. It was opened and endarterectomy performed back into the aorta. The posterior descending artery vein graft was anastomosed to the endarterectomized proximal RCA, and the remaining two vein grafts were brought off this graft in end-to-side fashion (Fig 2). Postoperatively the patient did well, and arteriography on the eighth postoperative day revealed good flow through the vein grafts. The saphenous vein graft to the small diagonal branch was occluded.

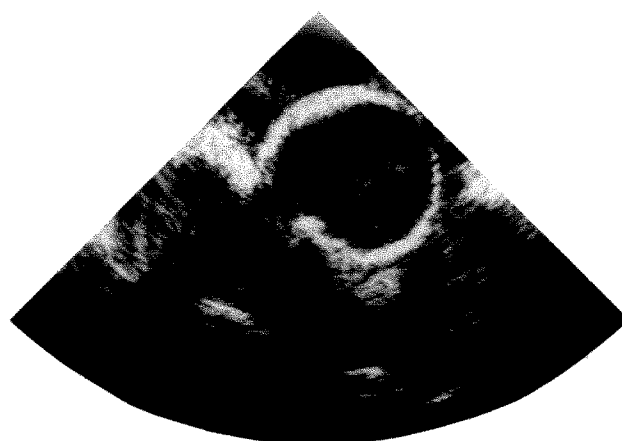


Fig 1. Epicardial echogram of ascending aorta with circumferential calcification.

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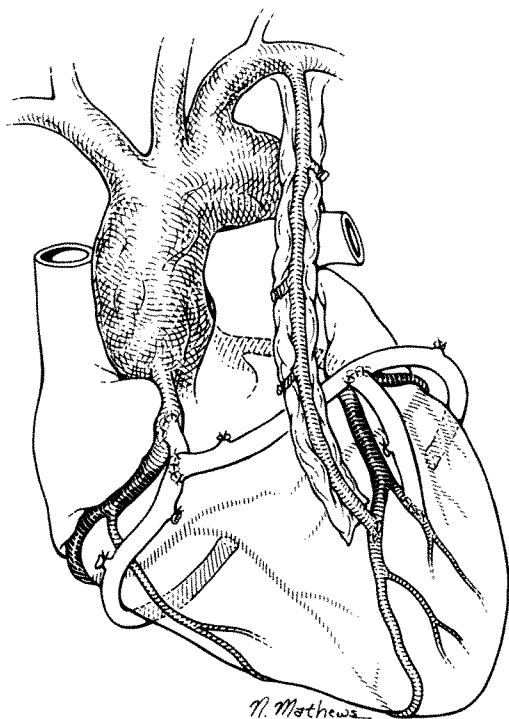


Fig 2. Proximal anastomotic site to the proximal right coronary artery with sequential grafts to the marginal and diagonal arteries.

Comment

Intraoperative discovery of severe aortic and arch disease presents a challenging dilemma but an opportunity for creativity. Often these patients have severe generalized vascular disease as well as difficult coronary anatomy. Various options have been reported in the literature, as well as a few nonreported anecdotal cases requiring closure of the patient and aborting revascularization. Suma [1] recently reported a "no-touch technique" using arterial conduits and fibrillatory arrest. In his report of 3 patients, all men, a successful result was obtained. Our case differed in that the patient was a small, brittle diabetic woman with a previous abdominal operation. We

thought that complete arterial conduit usage was not an option and would have unnecessarily prolonged the operative procedure. The left IMA was not adequate in diameter to be used as a proximal anastomotic site or for sequential grafting as recommended by others [3]. Hypothermic fibrillatory arrest worked well using the recommendations of Akins [4]: maintaining a high perfusion pressure near 80 mm Hg and left ventricular venting.

Because of the circumferential and inclusive nature of the aortic calcification, we did not believe it would be a safe alternative to resect a portion of the aorta with application of a pericardial or prosthetic patch for a proximal anastomotic site as discussed by Robicsek and Rubinstein [5].

Because the anterior portion of the proximal RCA was easily accessible, this vessel was opened approximately 2 cm from the aortic ostia and endarterectomized. It proved to be of generous size and, therefore, was used as the proximal anastomotic site. The remaining vein grafts were then anastomosed to the posterior descending artery vein graft (see Fig 2). Postoperatively, coronary angiography was repeated and revealed excellent flow through the patent vein grafts.

This case report describes an alternate method of revascularization for difficult patients in whom a porcelain aorta and substantial arch and great vessel disease are discovered at operation.

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Malignant Melanoma Metastatic to the Esophagus

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Malignant melanoma metastatic to the esophagus, as the only evidence of disease, is rare. We present the only known case treated at our institution and review 10 other cases reported in the world's literature. Of 11 patients (including ours) with melanoma metastasizing to the

esophagus and no other known disease, no patient survived 1 year. With this dismal prognosis, the goal of therapy in these patients must be palliation of dysphagia.

(*Ann Thorac Surg* 1993;55:516-7)

Primary malignant melanoma of the esophagus is uncommon, the reported prevalence varying from less than 0.1% to 0.5% of all esophageal malignant tumors [1]. Metastatic involvement of the esophagus by melanoma, as the only clinical evidence of disease, is even less common. We were able to find only 10 reported cases since 1895 in a review of the world's literature [2-9]. Here we report a case seen at our institution.

A 37-year-old man had resection of Clark's level IV melanoma of the upper back, and left axillary dissection, in September 1983. All lymph nodes as well as margins of resection were negative for tumor. In November 1983, he noted progressive dysphagia to solids. Barium swallow was performed and revealed a polypoid mass defect in the distal one third of the esophagus. Biopsy was done and interpreted as metastatic melanoma. Computed tomographic scan of the brain, chest, and abdomen and radionuclide bone scan showed no evidence of other metastatic disease. In December 1983, the patient underwent an esophagogastrectomy by the Ivor-Lewis approach. Exploration of the abdomen revealed no evidence of nodal or liver involvement. During the thoracic esophageal dissection, enlarged periesophageal lymph nodes were found and removed with the specimen. The patient was discharged 2 weeks after operation swallowing solids. Pathologic interpretation was malignant melanoma metastatic to esophageal muscle wall and submucosa with overlying ulceration, negative proximal and distal margins of resection, and melanoma metastatic to one of three periesophageal and ten of 19 perigastric lymph nodes. He did well until October 1984, when dysphagia recurred. He died in November 1984 of diffuse metastatic disease.

Comment

Although metastases to distant sites from primary malignant melanoma are very common, there are only a few case reports of melanoma metastatic to the esophagus as the only evidence of disease [2-9].

Allen and Spitz [10] in 1949 established the criteria for the diagnosis of primary versus metastatic melanoma. Primary tumors originate from the basal layer of the esophageal mucosa, which shows conspicuous junctional changes such as are seen in malignant melanoma and junctional nevi of the skin. In melanoma metastatic to the esophagus, the metastasis is usually submucosal and polypoid. The mucosa is usually normal or secondarily ulcerated and lacks the junctional changes seen in primary esophageal melanoma.

In the 10 reported cases in the literature of melanoma metastatic to the esophagus (with no other sites of disease), no patient survived greater than 10 months. All patients eventually developed widespread distant disease and died (Table 1).

To evaluate the impact of resection in these patients, the data from our patient and the 10 from the literature were analyzed by the Kaplan-Meier method (Fig 1). As demonstrated in Figure 1, the prognosis for patients with metastasis to the esophagus from malignant melanoma, even as the only site of disease, is dismal. No patient survived greater than 11 months, with a median survival

Table 1. Literature Review of Malignant Melanoma Metastatic to the Esophagus as the Only Evidence of Disease

Author	Year	No.	Treatment	Survival (mo)	Status
Spiegelberg [7]	1895	1	No treatment	2	DOD
Raniere [6]	1941	2	No treatment	5	DOD
Dedeurwaerder [8]	1975	3	No treatment	3	DOD
Butler et al [4]	1975	4	No treatment	3	DOD
Krementz et al [9]	1975	5	Chemotherapy	6	DOD
Nelson and Lanza [5]	1978	6	No treatment	3	DOD
		7	No treatment	5	DOD
		8	No treatment	<1	DOD
Wood and Wood [3]	1985	9	Resection & chemotherapy	10	DOD
Eng et al [2]	1989	10	Resection	8	DOD
Schneider et al (present report)	1993	11	Resection	11	DOD

DOD = dead of disease.

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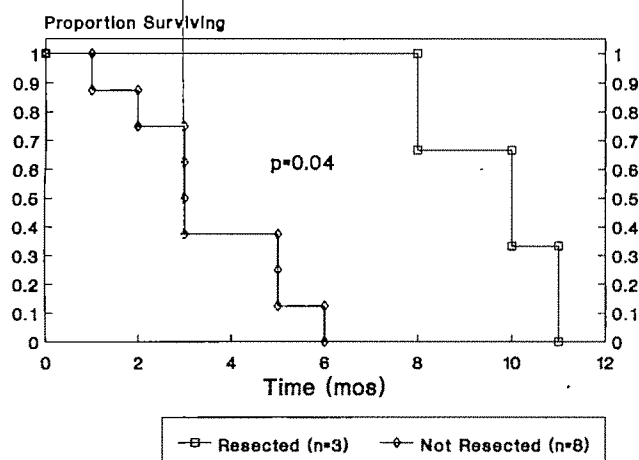


Fig 1. Actuarial 5-year survival (Kaplan-Meier method) and resection status of 11 patients with melanoma metastatic to the esophagus (p value by log-rank analysis).

of only 5 months for the entire series. However, the patients who were treated by resection survived significantly longer.

Although review of the literature yielded only 11 patients (including the one we report here) with malignant melanoma metastatic to the esophagus as the only site of disease, a few observations seem apparent: (1) metastasis to the esophagus, even though apparently the only site of disease, is a harbinger of disseminated disease; (2) once patients present with a metastasis to the esophagus, the prognosis is grave; and (3) local therapy appears to offer a slight survival advantage. With these observations in mind, certain guidelines for treatment are apparent: (1) esophagogastrectomy may be warranted in selected pa-

tients; (2) palliation of symptoms, particularly dysphagia, is the goal; and (3) better chemotherapeutic regimens are sorely needed to prolong life.

Currently, we would recommend esophageal dilation, laser resection, or an endoesophageal prosthesis as the preferred palliation for these patients. Esophagectomy may be warranted for select patients with good performance status.

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Primary Hemangiopericytoma Presenting as a Pancoast Tumor

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An intrathoracic extrapulmonary hemangiopericytoma presenting as a Pancoast's tumor, an unusual association, is presented.

(*Ann Thorac Surg* 1993;55:518-9)

A 53-year-old woman was admitted to the Royal Brompton Hospital with a 14-month history of left shoulder pain radiating down her arm. A previous chest roentgenogram was reported as normal 1 year before. At presentation a repeat chest roentgenogram showed a shadow at the extreme apex of the left lung with destruction of the second rib. She had a Horner's syndrome but no obvious muscle wasting. A computed tomograph showed, in addition, involvement of the second vertebral body and spinal end of the second left rib (Fig 1). All other investigations were normal.

At thoracotomy the tumor was in the apex outside the pleura, involving the second rib and infiltrating the vertebral body. The lung was not involved. The bulk of the tumor was excised, and after a normal postoperative recovery the patient was referred to the Royal Marsden Hospital for radiotherapy. She was given a dose of 60 Gy over a period of 6 weeks. When seen 2 years later she was pain free without evidence of recurrence.

Macroscopic analysis of the resected specimen revealed a smooth, encapsulated mass measuring $6 \times 4 \times 2$ cm with attached soft tissue and part of the left second rib which was infiltrated by tumor. The cut surface was smooth, soft, and pale brown and surrounded the rib. Microscopic examination showed round and spindle cells with pale pleomorphic nuclei. These cells surrounded slitlike vascular spaces giving a staghorn appearance to the vessels as typically seen in hemangiopericytoma (Fig 2).

Reticulin staining delineated the subendothelial basal lamina and surrounded small groups of cells (Fig 2, insert). Desmin, leukocyte common, and keratin markers were negative. The tumor cells were immunoreactive for vimentin. Anti-factor VIII-related antigen delineated normal endothelial cells, which lined the sinusoidal vascular spaces. Tumor cells extended beyond the tumor capsule, and there was vascular invasion. The mitotic count was 3

to 5 per 10 high-power fields. Electron microscopy showed that a minority of tumor cells were rich in fine filaments and the majority had an incomplete basal lamina, features compatible with hemangiopericytoma. There was no evidence of any other type of differentiation at the electron microscopic level.

Comment

The light microscopic, immunohistochemical, and electron microscopic features of this patient's tumor are typical of hemangiopericytoma [1]. Hemangiopericytomas are rare tumors that arise in soft tissue and can infiltrate bone. The most common sites of origin are the thigh and pelvic peritoneum [2]. More than 60 primary hemangiopericytomas have been described in the lung, but they are very rare outside the lung within the thorax [3, 4]. A collective study in 1964 [5] described 10 cases arising in the upper part of the thorax, mainly in the mediastinum. None were said to cause Pancoast's syndrome, although 1 patient had Horner's syndrome. No histology was demonstrated. Six cases proved malignant, whereas the remaining four were localized and encapsulated. Since then two further cases have been reported [6]. Both originated from an intercostal space and appeared malignant. The tumor in our patient originated in the second intercostal space; as it showed mitotic activity, vascular invasion, infiltration of a rib, and extension outside the capsule, it was considered malignant [3]. Surgical excision followed by radiotherapy appears to be the best treatment [5], and our patient was symptom free at 2 years.

Pancoast's syndrome is now often interpreted liberally. In 1932 Pancoast [7] introduced the term *superior sulcus tumor* to describe a tumor occurring "at a definite location at the thoracic inlet," and with a roentgenographic appearance showing "a small homogenous shadow at the extreme apex" associated with "more or less rib destruction and often vertebral infiltration." He pointed out that these patients had a "constant and characteristic clinical phenomena of pain in the eighth cervical and first and second thoracic trunk distribution . . . and Horner's syndrome." He stated that these tumors should not be confused with tumors arising at the apex of the lung.

Most tumors described as causing Pancoast's syndrome have been primary carcinomas of the lung, but others have included mesothelioma, Hodgkin's lymphoma, multiple myeloma, thyroid carcinoma, and metastatic tumors

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Fig 1. Computed tomographic scan of left apex showing destruction of second rib and erosion of vertebral body (arrow).

[8]. Nonneoplastic causes are rare and include tuberculosis, fungal infection, and hydatid disease [8].

The interesting feature of this patient is that she so clearly follows the pattern described by Pancoast in 1932. Pancoast thought that the behavior of these tumors was atypical for lung carcinoma because they lacked metastases to other sites as is common in lung tumors. All his cases had a fatal outcome with local disease infiltration. He postulated "a lack of origin from the lung, pleura, ribs or mediastinum" and suggested that the origin was possibly from some extrapulmonary structure. This case of hemangiopericytoma clearly fulfills Pancoast's criteria of a superior sulcus tumor. In addition, the use of resection followed by radiotherapy gave good results with prolonged survival.

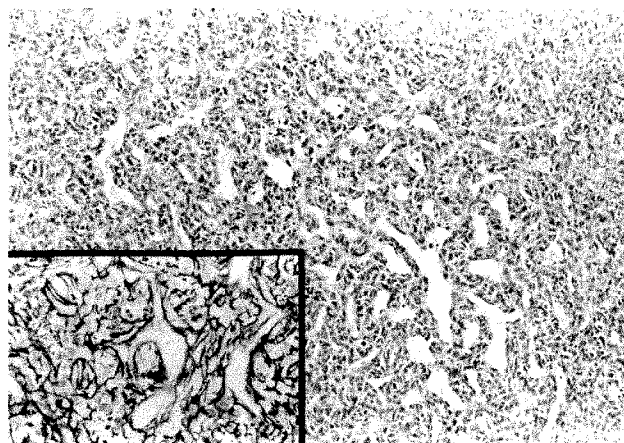


Fig 2. Section of tumor showing spindle cells surrounding slitlike (staghorn) vascular spaces ($\times 150$ before 50% reduction). Insert shows a reticulin stain with outlining of the subendothelial basement membrane and individual cells surrounded by fibers.

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Surgical Repair of Aorto–Right Ventricular Tunnel in an Infant

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A rare case of aorta to right ventricle tunnel with associated pulmonary stenosis was corrected on cardiopulmonary bypass in a 3-month-old infant. Both the aortic and ventricular openings were closed with a patch. Although the repair was successful and the child was discharged from the hospital, septicemia developed and she died later. Early repair of this defect is recommended.

(Ann Thorac Surg 1993;55:520–2)

Aortoventricular tunnel (AVT) is a rare congenital malformation presenting as aortic insufficiency and severe congestive heart failure in the neonate or young infant.

In some 50 previously reported cases of AVT, communication was between the right coronary sinus and the left ventricle [1–5]. Two articles report 1 case each of aorto–right ventricular tunnel: 1 in a neonate who died 6 hours after birth and another in a 10-year-old child who was successfully operated on [6, 7]. Here we report correction of aorto–right ventricular tunnel in an infant.

The patient was born after a normal pregnancy at full term to nonconsanguineous parents with no clinically significant past family history. Birth weight was 4.3 kg. A murmur was noted at birth, and a diagnosis of “ruptured sinus of Valsalva aneurysm” was made by echocardiography on the third day of life at the University Children’s Hospital, Bonn. Symptoms of congestive heart failure were treated with digoxin and diuretics, and the patient was discharged home. Recurrent lung and urinary tract infections subsequently developed. Cardiac catheterization at the age of 5 days confirmed the diagnosis of aortoventricular communication (Fig 1). In addition, a valvular right ventricular outflow tract gradient of 60 mm Hg was noted. At the age of 3 months the patient was transferred to London for semiurgent operation. Bacterial pharyngitis precipitated severe congestive failure and led to intubation and ventilatory support of the patient.

On admission, a 4/6 systolic murmur was noted. Pulses were “bounding.” The child was pale and gray, tachypneic (100 breaths/min) and tachycardic. Electrocardiography showed right ventricular hypertrophy. Chest roentgenogram revealed severe cardiomegaly and pulmo-

nary plethora. Oxygen was administered through nasal prongs, central venous and arterial monitoring was instituted, and the child’s condition was stabilized. Operation was organized for the following morning, October 1, 1991. Through a midline sternotomy, the thymus was partially excised and the pericardium was opened. The heart was grossly enlarged. A communication was noted arising from behind the right side of the dilated aortic root, passing leftward toward the base of the heart. The aorta and the right atrium were cannulated, and standard hypothermic cardiopulmonary bypass was instituted. The aorta was cross-clamped, and crystalloid cardioplegia (20 mg/kg) was administered into the root of the aorta while the “tunnel” was occluded with forceps.

A standard oblique aortotomy was performed. The aortic valve appeared to be rotated about 90 degrees clockwise, so that the left coronary artery was situated anterior to its normal position. The left coronary artery was probed, but the right coronary artery was not visualized. Dilatation of the aortic root at the juncture of the right and noncoronary sinuses was noted. A supraannular orifice approximately 1 cm in diameter communicated from the base of the dilatation to the extracardiac chamber. It was closed with a Gore-Tex (W. L. Gore & Assoc, Flagstaff, AZ) patch and 6-0 Prolene (Ethicon, Somerville, NJ). Care was taken not to distort the aortic valve leaflets or the left coronary orifice.

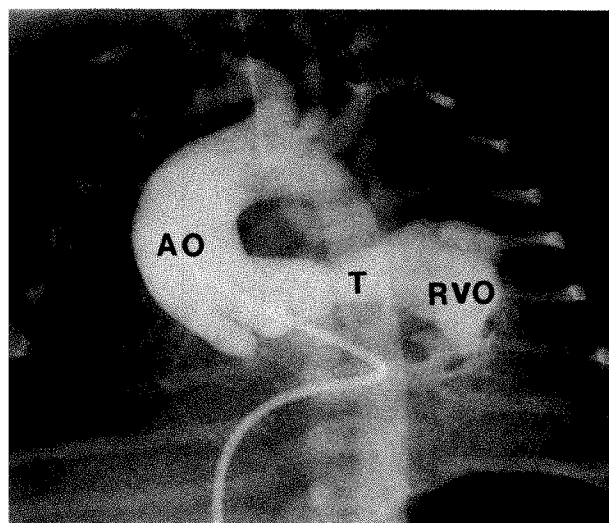
The right ventricular outflow tract was then opened with a short oblique incision. A large, posterior infundibular “defect,” approximately equal in diameter to the pulmonary valve orifice, was noted. This orifice appeared to be lined with normal ventricular endocardium. No evidence of inflammatory changes or ruptured aneurysm was seen. This defect, which was the ventricular opening of the tunnel, was closed with a Gore-Tex patch and running 5-0 Prolene suture, followed by aortotomy closure.

The ventricular wall was extremely thick, measuring about 3 cm. The muscle was pale and showed some fibrotic changes. Some muscle bands were excised, and the anterior wall of the right ventricle was thinned. The pulmonary valve was stenotic, and commissurotomy was performed. The aortic clamp was then removed and the patient was completely rewarmed. After ventriculotomy closure, bypass was discontinued and protamine given.

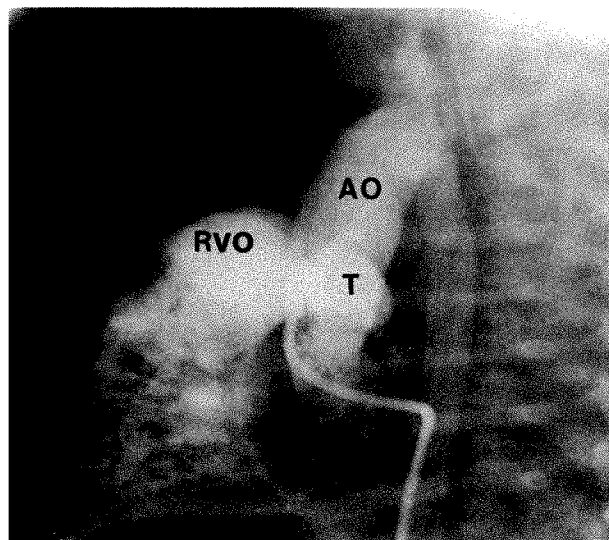
The hemodynamics were satisfactory, with an arterial systemic pressure of 90 mm Hg and a right atrial mean pressure of 6 mm Hg. Arterial blood gas analysis showed a pH of 7.37, carbon dioxide tension of 22 mm Hg, and oxygen tension of 452 mm Hg. During rewarming severe

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A



B

Fig 1. (A) Injection into the ascending aorta (AO) demonstrates the tunnel (T), which empties into the right ventricular outflow (RVO). (B) Lateral projection of the injection into the ascending aorta shows that the tunnel connects the aorta to the right ventricular outflow.

arrhythmias developed, including complete heart block and recurrent ventricular fibrillation. This instability continued after the bypass had been discontinued. Eventually the child returned to normal sinus rhythm. Recurrent ventricular fibrillation was controlled with a lignocaine infusion. The chest was splinted and the skin closed with a silicone rubber membrane, leaving the sternum opened.

Because of the severe ventricular hypertrophy and poor preoperative ventricular function, the patient was kept ventilated on a regimen of dobutamine drip, digoxin, and diuretics. The arrhythmias resolved and the chest was closed on the third postoperative day. Subsequently line sepsis developed, which responded well to the appropriate antibiotics. Administration of catecholamines was

discontinued very gradually because the left ventricular function remained impaired. The child was extubated on day 13. The final Doppler echocardiography showed much improved biventricular function. There was a residual gradient from the right ventricle to the pulmonary artery of 36 mm Hg. No aortic insufficiency was noted. C-reactive protein level returned to normal, and the white blood cell count before discharge was $13.9 \times 10^9/L$. The child was discharged home to Germany 20 days after operation on furosemide, 3 mg daily; captopril, 0.5 mg three times a day; and digoxin.

Five days after discharge the child had a fever and was readmitted to the University Children's Hospital, Bonn. Two-dimensional echocardiography showed vegetations on the patch. The child's condition became toxic and, despite intensive antibiotic therapy and resuscitation, she died 10 days after admission. Permission for postmortem examination was not granted by the family.

Comment

The clinical and pathological features of AVT considerably overlap those of ruptured sinus of Valsalva aneurysm. They have even been grouped together as "aorto-cardiac fistula" [8]. It has been suggested that AVT may represent in utero rupture of a sinus of Valsalva aneurysm [9, 10]. Aortoventricular tunnel often presents in the first few days of life [2], whereas ruptured aneurysm of the sinus of Valsalva is more common in the second to fourth decade of life [8]. The AVT is of the same consistency and thickness as the aortic wall and is associated with an externally visible structure that may even be seen as an extracardiac bulge on a chest roentgenogram [1]. The AVT then passes through the septum behind the right ventricular infundibulum to enter the left ventricle. In rare cases such as the one presented here, the AVT enters the right ventricle. In contrast, ruptured aneurysm of the sinus of Valsalva is a thin-walled, narrow outpouching running an entirely intracardiac course to the cardiac chamber. The entrance is most often in the form of a perforated wind-sock [8]. To distinguish between AVT and ruptured sinus of Valsalva aneurysm may not be clinically, echocardiographically, or angiographically possible. It is, however, not important, as both conditions should be treated surgically.

We believe that the treatment should be undertaken in the neonatal period or as soon as the diagnosis is made. The clinical course of our patient would support this recommendation. Although the patient's heart failure was initially controlled, severe ventricular hypertrophy subsequently developed. That was most likely the cause of severe postoperative arrhythmias and initially impaired ventricular function. In addition, the patient suffered several infective episodes, which are always more difficult to treat in an infant in severe heart failure. Whether the final infection was related to these episodes or to the last episode of postoperative line sepsis, or whether it was entirely independent of these is open to discussion.

In conclusion, we have presented an infant with rare aorta to right ventricle tunnel. Although the repair was successful, the child died later in severe septic shock. We recommend early surgical repair for patients with AVT.

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Sequestration of the Left Coronary Artery From the Aorta

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A patient with the left coronary artery isolated from the ascending aorta is discussed. This is the seventh case described and the third diagnosed preoperatively. In contrast to other patients she had predominant aortic incompetence and was much older (52 years compared with the other patients, all younger than 25 years). She also had two angiograms demonstrating progressive iso-

lation of the coronary artery with time. The patient was managed by aortic valve replacement. It is our belief that the condition is acquired and resulted from fusion of the free edge of the aortic valve leaflet to the supravalar ridge secondary to an inflammatory process.

(*Ann Thorac Surg* 1993;55:523-4)

A 45-year-old woman was admitted initially in 1983 with dyspnea and chest pain. There was a history of rheumatic fever as a child and previous treatment for pulmonary tuberculosis. Investigations including cardiac catheterization confirmed aortic valve regurgitation and almost complete isolation of the left coronary artery, except for a small communication, from the aorta. Surgical correction was advised but was declined by the patient.

In 1990, when 52 years old, she was readmitted with similar symptoms. She was undistressed with no features of infective endocarditis. The pulse was regular and the blood pressure was 150/60 mm Hg. The apex of the heart was laterally displaced. The first heart sound was soft with an ejection click present. A systolic ejection murmur and a soft early diastolic murmur were heard at the base of the heart and along the left sternal border.

The electrocardiogram demonstrated sinus rhythm, right bundle-branch block, left-axis deviation, and signs of left atrial enlargement. The cardiac silhouette was enlarged on chest roentgenogram.

A 10-mm Hg peak to peak gradient across the aortic valve was measured at catheterization. The valve was not calcified, and the aortic root was dilated. Severe aortic regurgitation was evident, but the ventricle contracted well and was not dilated. The left coronary artery could not be entered. The right coronary artery was a widely patent dominant vessel. A very large conal branch arising from the proximal right coronary artery filled the unobstructed left coronary artery system. Retrograde filling of the left coronary artery showed delineation of a rudimentary left valvar sinus (Fig 1).

During cardiopulmonary bypass with moderate hypothermia and crystalloid cardioplegic arrest the anatomy was defined through a transverse aortotomy. Large right and noncoronary cusps with slightly thickened edges

were found. In the position of the left coronary cusp a domed structure, which appeared to be thickened valve tissue, was completely fused with the supravalar ridge (Fig 2). No egress of blood or cardioplegia could be demonstrated. An incision exposed a valve sinus with a small but patent left coronary artery ostium at the base. No thrombus was present. The valve was replaced with a 25-mm tilting disc prosthesis. Her postoperative course was uneventful.

Comment

Adhesions of the free edge of an aortic valve leaflet to the aortic wall have been well documented. However, this is mostly associated with supraaortic stenosis. In fact, cusp abnormalities were present in more than a third of cases reported in a review of supraaortic stenosis by Rastelli and associates [1]. Underdevelopment of the left coronary cusp was noticed most commonly, but partial cusp adhesions were seen frequently by Flaker and colleagues [2].

Complete isolation of the coronary cusp and the coronary artery in patients with supraaortic stenosis has been described four times [3-6]. Two left and two right coronary cusps were involved. Only one [5] was recognized preoperatively on angiography, the other three being noted at autopsy.

Two further cases have been described [7, 8]. Waxman and co-workers [7] reported isolation of the left coronary artery in a patient with aortic stenosis and regurgitation. A 16-year-old girl presented with syncope and chest pain. There was no history of an inflammatory process. Cardiac catheterization revealed moderate aortic valve regurgitation and a 20-mm Hg gradient across the aortic valve. An isolated left coronary sinus filled retrogradely through the right coronary artery and collaterals. The indication for operation was angina, and at operation the cusp was freed. Follow-up examination and catheterization were normal. Although it was not histologically proven, Waxman and co-workers speculated that their case was a forme fruste of supravalar aortic stenosis.

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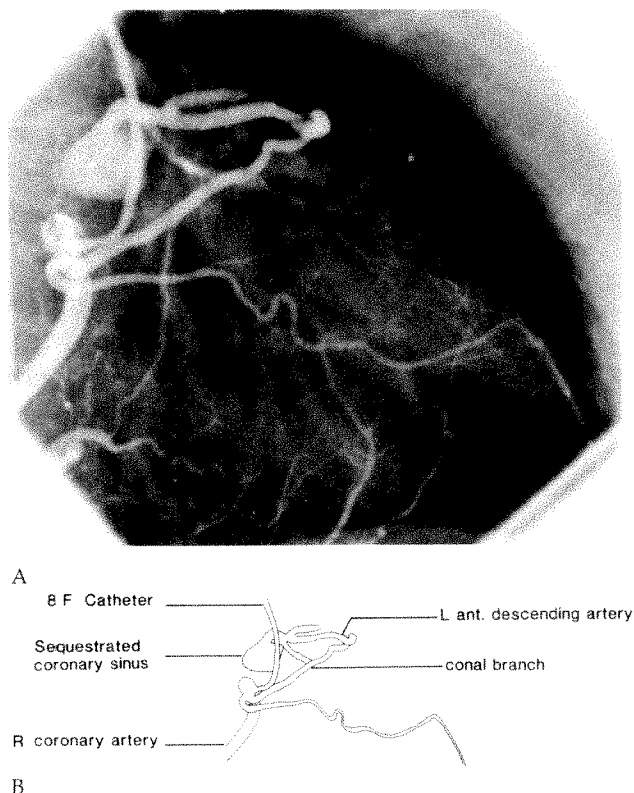


Fig 1. Catheterization of right coronary artery demonstrating filling of the left coronary system and left sinus of Valsalva through a large caval branch.

The question still remains whether isolation of the left coronary ostium is acquired or congenital. The absence of initial signs and the thickened cusps tend toward a gradual inflammatory process involving the valve cusps with adhesions to the aortic wall, but also may be ascribed to a congenital abnormality of the leaflet tissue. In two reports [7, 8] the consensus leaned toward a developmental abnormality. We believe that in our patient it was

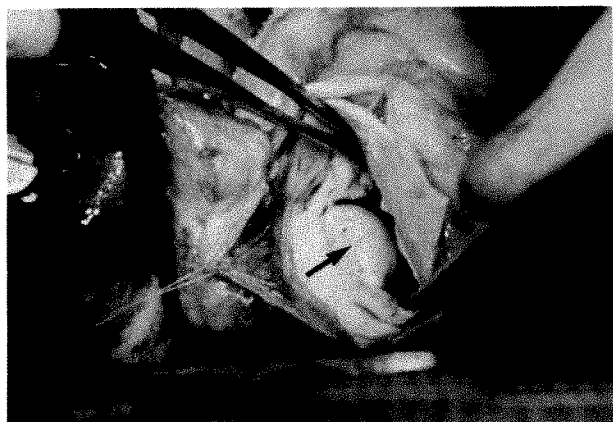


Fig 2. Surgeon's view of domed structure in left sinus of Valsalva.

probably acquired. A heart murmur was noticed 25 years before, and she became symptomatic late in life. There is a history of rheumatic fever as a child, although in isolated aortic valve disease one should also consider nonrheumatic aortic root disease. Over a 7-year period the left coronary ostium progressed from a small communication between the aortic root and left coronary sinus to a complete seal. Unfortunately, the first angiogram was inadvertently destroyed, but the catheterization report is adamant in the description of the left coronary artery filling retrogradely from the right and communicating with the aortic root. One of us (R.F.) performed the first angiogram. Varying degrees of adherence of valve cusps to the aortic wall have been described [2]. Histologic examination of the thickened cusps in our case was unhelpful.

Under normal circumstances one would expect a blind-ending vessel to thrombose and obliterate, but compression of the sinus during systole with to-and-fro movement of blood in and out of the sinus during the cardiac cycle probably prevented stasis formation. This was noticed by Waxman and co-workers [7] as well.

Adhesions of aortic valve cusps are common in the rare condition of supra-ventricular aortic stenosis. Complete isolation has been described in 4 patients with supra-ventricular aortic stenosis. This phenomenon was also seen in a patient with quadricuspid aortic valve and could represent a congenital defect [8]. Although the patient of Waxman and co-workers had associated aortic regurgitation, operation was for angina and syncope. Our patient was operated on for pure regurgitation with late onset of symptoms and signs, and no evidence of stenosis. A preoperative diagnosis was possible and a relatively simple operation gave good results.

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Angiosarcoma of the Heart Causing Cardiac Rupture: A Rare Cause of Hemopericardium

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Cardiac rupture as a complication of primary cardiac tumors has rarely been reported in the literature. The diagnosis is difficult to establish preoperatively, but echocardiography may provide the best assessment of cardiac damage. We found a loculated pericardial effu-

sion on two-dimensional echocardiography, a finding that has been documented in two of the previous four case reports. A case of right atrial rupture is reported with review of other cases from the literature.

(Ann Thorac Surg 1993;55:525-8)

Angiosarcomas are the most prevalent primary malignant cardiac tumors, accounting for 20% of all cardiac malignancies [1]. The presentation of angiosarcoma is usually late, when the tumor begins to limit cardiac output by mechanical obstruction. However, most tumors are locally invasive, so local resection or transplantation may still be a therapeutic option [2]. Cardiac rupture remains a rare complication of primary heart tumors, but cases of cardiac rupture secondary to metastatic involvement of the heart by other malignancies has been described [3]. We report a case of right atrial rupture secondary to a primary cardiac angiosarcoma that was not diagnosed preoperatively despite echocardiography and computed tomographic scanning.

A 47-year-old man presented to his local hospital with a 5-week history of breathlessness and dull chest pain. On admission he was found to have a swinging pyrexia of up to 38°C. On examination, he had no palpable lymph nodes, but was clinically anemic. Cardiovascular examination found the signs of cardiac tamponade: pulse, 120/minute; blood pressure, 110/60 mm Hg with a pulsus paradoxus of 15 mm Hg; jugular venous pressure, 7 cm H₂O, cardiac sounds faint but normal, and the apex beat shifted to the midaxillary line. Respiratory, abdominal, and neurologic examinations were normal. Hematologic tests revealed a normochromic normocytic anemia of 9.4 g/dL (normal, 13.0 to 18.0 g/dL), a mild neutrophilia of $10 \times 10^5/L$ (normal, 2.0 to $7.5 \times 10^5/L$), and a normal platelet count. A chest roentgenogram found a large heart with a globular cardiac silhouette. A two-dimensional echocardiogram showed a loculated effusion.

After 10 days as an inpatient he was discharged home because of reduction in his symptoms and a repeat echocardiogram that had shown a substantial decrease in the size of his effusion from 4 cm to 1 cm. However, he returned to his local hospital 3 weeks later after an

episode of collapse. On readmission, echocardiography was unchanged. Two pericardiocenteses via the sub-xiphisternal approach were unsuccessful in obtaining pericardial fluid. He was transferred to another hospital. A computed tomographic scan showed a poorly defined mass lying anteriorly over the heart in the superior part of the mediastinum; it was not possible to discern if this was a loculated part of the pericardial cavity, but there was no pericardial effusion inferiorly. Metastatic lesions were also noted in the lungs. He was urgently transferred to the Hammersmith Hospital for the establishment of a tissue diagnosis. His clinical state had seriously deteriorated, and he now had intractable dyspnea. A two-dimensional echocardiogram with color Doppler flow imaging showed a large, loculated pericardial effusion surrounding the right ventricular free wall and base of the heart. Intracardiac anatomy was normal, but there was an ill-defined mass surrounding the right ventricular inflow tract, constricting and compressing the tricuspid annulus and extending both anteriorly and posteriorly, invading the right ventricular walls and right atrium (Fig 1). Color Doppler flow failed to identify a communication between the right atrium and the pericardial cavity. Right ventricular function was poor, with diastolic compression of the right ventricular outflow tract; left ventricular function was normal.

He was submitted for operation. At median sternotomy, a hemopericardium was evident. On opening the pericardium a large volume of blood was lost and the systolic blood pressure fell to 30 mm Hg. A hole was found in the right atrium at the junction of the superior vena cava, which was approximately 2 cm in length. Hemorrhage was controlled by placing a digit in the rupture, and the patient was transfused blood and colloid. The pressure returned to the preoperative level of 90 mm Hg systolic. On assessment, the tumor was invading most of the right atrium and was involving the right ventricle and the superior and inferior venae cavae. The edges of the right atrial rupture were diaphanous and

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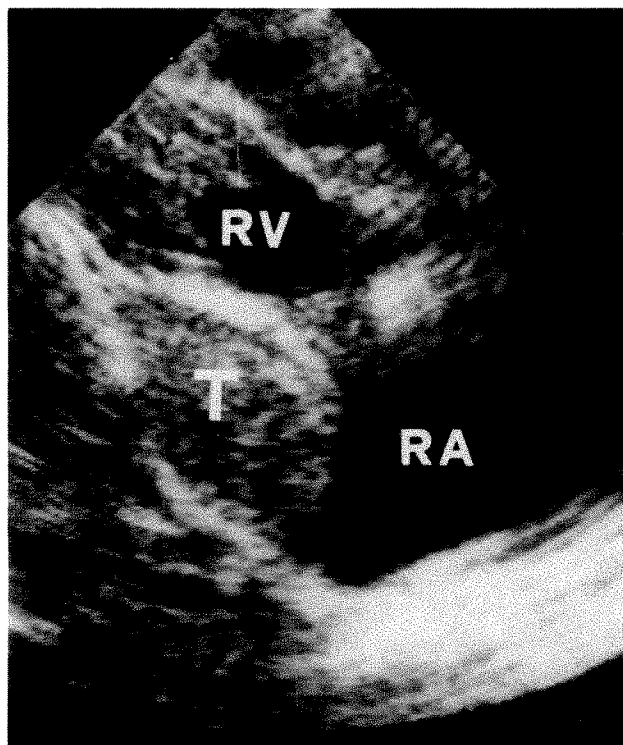


Fig 1. Right ventricular inflow tract view showing a large mass compressing the tricuspid annulus. The right ventricular free wall was somewhat thickened and homogeneously echogenic with global hypokinesia suggestive of myocardial infiltration by the tumor. (RA = right atrium; RV = right ventricle; T = tumor.)

involved by tumor. The majority of the pericardial cavity was obliterated by tumor and adhesions, except for an area around the free wall of the atrium. Blood had been escaping from the right atrium and entering a loculation within the pericardial cavity. A biopsy of the tumor was performed. In view of the advanced stage of the disease, localized resection under cardiopulmonary bypass was not undertaken. The walls of the atrium would not have accepted a Dacron patch, and the available pericardium was also involved with disease. The atrial rupture was enlarged digitally and the pericardium closed, thus creating a neo-right atrial appendage. A postoperative two-dimensional echocardiogram showed that the right ventricular outflow tract was no longer compressed in diastole, and clinically this was correlated with a reduction in his dyspnea. He was assessed by the oncology team, who concluded that chemotherapy and radiotherapy were inappropriate given the nature of the tumor and its advanced stage. Histologic examination of operative biopsy specimens found the tumor to be an angiosarcoma.

The patient died 22 days postoperatively of advancement of his cardiac disease. This was confirmed by autopsy, which found an angiosarcoma originating near the annulus of the tricuspid valve and extending to invade the right ventricle, most of the right atrium, the superior vena cava, and pulmonary artery. The tumor had exten-

sively invaded the pericardium, and metastatic nodules were identified in both lungs but in no other part of the body.

Comment

Cardiac rupture due to angiosarcoma is extremely rare; 4 other cases, all involving the right atrium, have been reported in the literature to date [4-7]. The presentations (Table 1) have been diverse, from nonproductive cough and chest pain [4] to bilateral pneumothoraces [5], supraventricular tachyarrhythmia [6], and bloody pleural effusion [7]. In our patient, breathlessness was the main complaint on presentation. This was due to the size of the tumor and obstruction of the right atrium and ventricle as demonstrated by echocardiography. Of the 4 previously reported patients only 2 survived to have the diagnosis confirmed at operation, and only in 1 patient reported by Satou and associates [7] was the diagnosis truly established by preoperative investigations. In this patient blood was seen leaving the right atrium and circulating within the pericardial cavity on color Doppler and contrast two-dimensional echocardiography. In our patient, using similar scanning techniques, we were unable to find a rupture point preoperatively. The most frequently reported echocardiographic finding in cases of cardiac rupture has been a loculated pericardial effusion. This echocardiographic sign was found in the present case and in 2 of the 4 previously reported cases (see Table 1). The loculations may be a desmoplastic response to the tumor, inflammation, and adhesion formation secondary to neoplastic infiltration or a response of the pericardium to the chronic exposure of blood and clot.

Because of the late presentation of patients with these tumors, up to 80% of cases have pulmonary metastases [1]. Nevertheless, this does not preclude surgical intervention. If the tumor can be locally excised, then this may still produce good palliation of symptoms. Heart or heart-lung transplantation may be considered for those patients with disease limited to the heart or those with metastases limited to the lungs [8]. None of these surgical options was appropriate for our patient, but postoperatively his dyspnea was substantially improved. We can only postulate that this was a result of creating a larger defect in the right atrial wall, which allowed the blood to circulate freely within the pericardial cavity without compressing or tamponading the right ventricular outflow; this improvement was demonstrated by postoperative echocardiography.

Anecdotal reports of long-term survival are present in the literature with adjuvant chemotherapy or radiotherapy, but no definitive studies are available due the rarity of the malignancy. Recently, Putman and associates [2] retrospectively reviewed their 25-year experience with cardiac sarcomas, which included 7 angiosarcomas, but could find no improvement in survival using doxorubicin-based chemotherapy.

Table 1. Cardiac Rupture Due to Angiosarcoma

Authors	Year	Age (y)	Sex	Presentation	Investigation	Operation	Autopsy	Outcome
Lutus & Stelzer	1983	24	M	Nonproductive cough & chest pain	2D echocardiography: loculated pericardial effusion, R atrial border discontinuous with shaggy edges, no blood demonstrated to leave R atrium	Rupture of right atrium, loculated hemopericardium; no other information	Not stated	Not stated
Lobo et al	1989	75	M	Hemoptysis, anorexia, chest pain; initially L pneumothorax, later R pneumothorax; sudden onset of dyspnea & hypotension; died	CT scan: mass in R atrium, metastases in both lungs	...	Angiosarcoma of R atrium with 0.5-cm perforation communicating with the R pleural cavity	Died
Lantz et al	1989	55	F	Syncope, hypotension, supraventricular tachycardia	2D echocardiography: pericardial tamponade; pericardiocentesis; 130 mL bloody fluid; died 3 hours later	...	Hemopericardium, 2 defects in R atrium 4 cm in length, angiosarcoma of R atrium & pericardium	Died
Satou et al	1991	41	M	Chest pain, R bloody pleural effusion	CT scan: R atrial mass; 2D echocardiography: loculated pericardial effusion; color Doppler: blood flow from RA to pericardial sac; coronary angiography: contrast passed from RA into pericardial sac	Hemopericardium, adhesions in pericardium, loculated effusion; RA rupture repaired with pericardial patch	Angiosarcoma invading R atrium & R ventricle, bloody pleural effusions & pulmonary metastases	Dyspnea & hemoptysis; died on 73rd postoperative day in hospital

CT = computed tomographic; F = female; L = left; M = male; R = right; RA = right atrial; 2D = two-dimensional.

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REVIEW OF RECENT BOOKS

John Gibbon and His Heart-Lung Machine

By Ada Romaine-Davis

Philadelphia, University of Pennsylvania Press, 1991

251 pp, illustrated, \$37.95

Reviewed by John C. Myers, MD

Recent graduates of cardiothoracic surgical training programs are fortunate to have used and taken for granted technology in cardiopulmonary bypass that allows for the completion of cardiac surgical procedures with lower operative mortality than many noncardiac thoracic operations. *John Gibbon and His Heart-Lung Machine* offers a personal look at a true pioneer and visionary whose work paved the way to the potential complacency of today's resident.

This well-written monograph ranges from anecdotes of Dr Gibbon's childhood to a detailed discussion of his animal and initial human experiences with his invention. From his early clinical exposure to pulmonary embolism as a surgical resident and the wish to support these patients during embolectomy, to his methodical development of a reproducible machine, to successful correction of an atrial septal defect, this monograph chronicles Gibbon's successes and failures in a highly readable fashion.

This book is a welcome addition to the library of cardiothoracic surgeons, cardiac physiologists, and those interested in surgical history. Read it with pleasure.

San Antonio, Texas

Postcardiotomy LVAD Support and Transesophageal Echocardiography in a Child

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A case of postcardiotomy cardiogenic shock after repair of a congenital ventricular septal defect in a 5-year-old boy is reported. Mechanical circulatory support, instituted with a centrifugal left ventricular assist device, adequately supported the patient for 50 hours until recovery of native left ventricular function occurred.

Transesophageal echocardiography proved to be useful in assessment of left ventricular function, allowing for timely institution and withdrawal of mechanical circulatory support.

(Ann Thorac Surg 1993;55:529-31)

Extracorporeal mechanical circulatory assistance has become a viable option for adult patients with postcardiotomy cardiogenic shock that is refractory to pharmacologic support. Infants and small children who experience postoperative ventricular dysfunction, however, have fewer treatment options. For example, size constraints, as well as increased aortic compliance, render the intraaortic balloon pump ineffectual in young patients [1]. Recent reports [2, 3] have indicated encouraging results using venoarterial bypass with an extracorporeal membrane oxygenator; however, the procedure for instituting support is labor intensive, and prolonged support is associated with major complications. We treated one of our pediatric patients who had postcardiotomy cardiogenic shock after repair of a congenital heart defect with an extracorporeal centrifugal ventricular assist device. Transesophageal echocardiography (TEE) was used to monitor left ventricular recovery, which enhanced the success of treatment.

A 5-year-old boy (20 kg) underwent surgical repair of a perimembranous ventricular septal defect. Preoperative examinations revealed a dilated left ventricle (end-diastolic dimension, 48 mm; shortening fraction, 0.38) and a redundant anterior leaflet of the tricuspid valve. Ventricular function was preserved (left ventricular pressure, 110/4 mm Hg; right ventricular pressure, 28/4 mm Hg). Pulmonary artery pressure was 28/10 mm Hg (mean, 16 mm Hg), and pulmonary artery wedge pressure was 8 mm Hg. Retrograde flow through the ventricular septal defect was causing tricuspid valvular dysfunction with a pulmonary-to-systemic blood flow ratio of 2:1. There was no evidence of aortic or pulmonary valve dysfunction.

At operation, total cardiopulmonary bypass was instituted with bicaval and aortic cannulation. The heart was

arrested with 15 mL/kg of standard Roe's cardioplegic solution at 6°C, and Dacron patch repair of the ventricular septal defect was accomplished (total ischemic time, 25 minutes). Attempts to wean the patient from cardiopulmonary bypass failed. Electrocardiography revealed a widened QRS complex and transitory third-degree heart block, and TEE revealed global left ventricular dysfunction with paradoxical septal motion. Air embolization to the coronary arteries was suspected and treated by briefly cross-clamping the aorta again and by providing inotropic support.

Despite maximal pharmacologic support and resumption of sinus rhythm, further attempts to wean the patient from bypass failed. Thus, mechanical circulatory support with a Bio-Medicus (BP50; Bio-Medicus, Minneapolis, MN) ventricular assist device was instituted. A 28F wire-reinforced right-angle cannula (Research Medical, Salt Lake City, UT) was inserted into the left atrium through the right superior pulmonary vein. Blood was returned to the ascending aorta through a 14F aortic cannula (Texas Medical Products, Houston, TX). Flow from the Bio-Medicus pump was maintained at 2 L/min (cardiac index, $2.6 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$), and the patient was weaned from bypass (total bypass time, 158 minutes), during which time TEE was used to gauge the degree of ventricular distention. No immediate cause for the ventricular dysfunction was apparent. Electrolytes within the cardioplegic solution were confirmed to be normal. The sternum was left open, and the skin was reapproximated with interrupted sutures.

During the next 24 hours, the patient's condition stabilized. Average pump flow was maintained at 2 L/min, and amrinone and nitroprusside were given to reduce afterload (left atrial pressure, 8 to 12 mm Hg). Postoperative bleeding was moderate, necessitating the transfusion of 3 units of packed red blood cells, 4 units of platelets, and 1 unit of fresh-frozen plasma during the first 24 hours of support. Mild hemolysis was present, as evidenced by a decrease in the plasma free hemoglobin level (from 34

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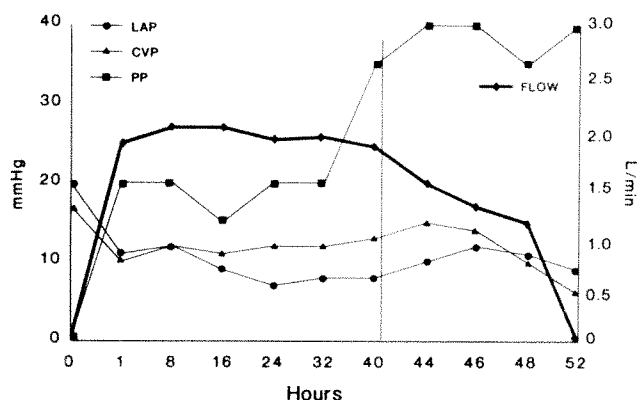


Fig 1. Evidence of left ventricular recovery consisted of increasing pulse pressure and stabilization of filling pressure as pump flow decreased. The weaning process began at 40 hours after support had been instituted. (CVP = central venous pressure; LAP = left atrial pressure; PP = pulse pressure.)

mg/dL after 4 hours of pump support to 29 mg/dL after 24 hours). Transesophageal echocardiography on postoperative day 1 revealed slight improvement in ventricular wall motion, continued antero-septal hypokinesia, and paradoxical septal motion. In addition, the left ventricular cavity remained distended (43 mm). The next day, systemic pulse pressure increased to 40 mm Hg, which indicated ventricular recovery. Before the weaning process was begun, systemic heparinization was instituted (400 U/h). Pump flows were progressively decreased to 1 L/min, at which time mean arterial pressure ranged from 65 to 75 mm Hg, without an increase in left atrial or central venous pressures (Fig 1).

After approximately 50 hours of pump support, the patient was returned to the operating room for completion of the weaning process and removal of the device. Intraoperative TEE revealed improvement of left ventricular contractility and of septal dyskinesia. Mitral and tricuspid valve functions were normal. The cannulas were removed, and the sternum was closed. The patient remained hemodynamically stable, and all pharmacologic support was stopped during the next 24 hours. No deterioration in renal or hepatic function was observed during circulatory support. The patient was weaned from mechanical ventilatory support the day after circulatory support had been discontinued. Repeat TEE showed good posterior wall motion with minimal septal motion (shortening fraction, 0.29).

The remainder of the patient's postoperative course was uneventful. He was able to ambulate and progressively returned to his normal functional level. On postoperative day 7, echocardiography revealed no residual ventricular septal defect and a dilated left ventricle (end-diastolic dimension, 42 mm); however, left ventricular function was normal (estimated shortening fraction, 0.35). The patient was discharged from the hospital and prescribed digoxin, captopril, and furosemide. Three weeks after operation, echocardiography revealed a left ventricular end-diastolic dimension of 42 mm and a shortening

fraction of 0.38. Posterior wall motion was normal, but septal dyskinesia persisted.

Comment

Our case shows the feasibility of treating children who experience postcardiotomy cardiogenic shock with an extracorporeal mechanical circulatory support device. The 5-year-old boy in this case received adequate circulatory support for approximately 50 hours, which allowed time for left ventricular recovery. No major complications occurred during or after operation. Although mild hemolysis was observed after the operation, it was probably related to the prolonged cardiopulmonary bypass time, not to left ventricular assist device support. Follow-up 3 weeks after the patient was discharged revealed improved left ventricular function.

Use of ventricular assist devices in children has been limited. Matsuda and associates [4] reported using a paracorporeal, pneumatically driven ventricular assist device in 3 pediatric patients (ages, 3 to 10 years) who experienced postoperative cardiogenic shock after repair of congenital anomalies. Two patients died of multiorgan failure during circulatory support, and the third died of respiratory failure 20 days after being weaned from the device. Three other patients (ages, 9 to 11 months) who experienced postcardiotomy shock received left heart support (duration of support, 5 to 13 days) with a centrifugal pump and were weaned from support; however, they died of infectious or thromboembolic complications [5]. Frazier and colleagues [6] reported use of a centrifugal pump for left heart support as a bridge to transplantation in a 9-year-old boy.

The success of mechanical circulatory support in our patient can be partially attributed to TEE. The development of smaller endoscopic probes has made TEE a useful technique for diagnosing and characterizing congenital cardiac anomalies in pediatric patients [7]. In addition, TEE is useful for gauging intraoperative repair and monitoring myocardial function [8]. In our case, TEE allowed accurate and timely assessment of left ventricular function and recovery, which permitted expeditious weaning from extracorporeal circulatory support. We believe that timeliness was instrumental in preventing major complications.

Our case demonstrates that extracorporeal circulatory support can be used effectively to sustain a pediatric patient during postcardiotomy cardiogenic shock. With the timely removal of such support, complications can be minimized and the patient returned to a normal level of activity.

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Notice From the American Board of Thoracic Surgery

The part I (written) examination will be held at the Hilton Executive Conference Center, Dallas Fort Worth Airport, Dallas, TX, on February 13, 1994. The closing date for registration is August 1, 1993.

To be admissible for the part II (oral) examination, a candidate must have successfully completed the part I (written) examination.

A candidate applying for admission to the certifying examination must fulfill all the requirements of the board in force at the time the application is received.

Please address all communications to the American Board of Thoracic Surgery, One Rotary Center, Suite 803, Evanston, IL 60201.

Warm Heart Surgery in Patients With Cold Autoimmune Disorders

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Continuous warm antegrade delivery of cardioplegia while maintaining systemic normothermia is a new method of performing coronary artery bypass grafting. It can be used to avoid the detrimental effects of hypothermia in patients with cold autoimmune disease.

(*Ann Thorac Surg* 1993;55:532-3)

Cryoglobulinemia is one of three primary cold autoimmune diseases. When patients with this disorder are cooled below a critical temperature, immunoglobulins precipitate in their serum [1]. This can cause systemic hyperviscosity, microvascular thrombosis, purpura, and progressive glomerulonephritis [1]. Current methods of performing cardiac operations on these patients require that serum immunoglobulins be removed by plasmapheresis preoperatively [2] or be flushed out of the coronary arteries by warm crystalloid cardioplegia before cold crystalloid cardioplegia is given [3, 4] or that operation be performed on the warm heart as it fibrillates without aortic cross-clamping [1]. We report the successful performance of a coronary bypass operation in a patient with documented cryoglobulinemia using systemic normothermia and continuous warm antegrade blood cardioplegia [5] in an effort to avoid the adverse effects of hypothermia. This technique is applicable to all cold autoimmune diseases.

A 69-year-old man with a 14-year history of angina (Canadian Heart Association classification IV) was admitted to our hospital with persistent anginal pain and electrocardiographic evidence of inferior myocardial ischemia. He received intravenous streptokinase therapy, and a myocardial infarction was documented with a total creatine kinase level of 4,000 U and a creatine kinase MB fraction of 500 U. Angina continued to occur at rest despite intravenous nitroglycerin therapy, oral β -blockers, and calcium-channel blockers. Cardiac catheterization revealed reduced left ventricular function and severe three-vessel coronary artery disease with 2+ mitral regurgitation. The day after angiography pain and tenderness in the legs developed, associated with a purpuric rash, which suggested a cutaneous vasculitis. Serum immune screening revealed the presence of cryoglobulins of the

immunoglobulin A- κ and immunoglobulin G families. A cryohematocrit was negative for hemagglutinins. Based on the patient's lower extremity rash and the finding of cryoimmunoglobulins in the serum, a diagnosis of primary cryoglobulinemia was made. The cryoglobulinemia crisis was thought to have been brought on by the cardiac catheterization, which used room temperature contrast agents. Because of persistent angina after a myocardial infarction associated with severe three-vessel disease, coronary artery bypass grafting was performed.

After median sternotomy and heparinization, the heart was cannulated through the ascending aorta and right atrium. The saline prime was recirculated through the heat exchanger at 37°C (Bard Membrane Oxygenator, Tewksbury, MA) to keep it from cooling before cardiopulmonary bypass was instituted. Bypass was instituted at normothermia using the technique described by Lichtenstein and associates [5]. With the heart empty and beating, a hyperkalemic blood cardioplegia solution was introduced into the root of the aorta at 37°C. The aorta was cross-clamped between the cardioplegia port and the aortic cannula. An initial arrest dose of 1,500 mL of high-potassium solution (potassium content, 20 mEq/L) was infused, followed by continuous low-potassium (potassium content, 7 mEq/L) blood cardioplegia into the aortic root and subsequently through vein grafts. Throughout the cross-clamp period, brief (5- to 10-minute) interruptions of cardioplegia administration occurred to facilitate the performance of the distal anastomoses.

Vein grafts were performed to the posterior descending artery and the circumflex marginal artery; the left internal mammary artery was used to bypass the left anterior descending artery. Proximal anastomoses were done with the aortic cross-clamp still in place. After removal of the cross-clamp, normal sinus rhythm returned spontaneously without need for defibrillation. Urine output on bypass was excellent. Because of transient worsening of mitral regurgitation the patient was placed on 5 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ of dopamine and weaned from cardiopulmonary bypass after 93 minutes. There were no electrocardiographic or enzymatic signs of perioperative myocardial infarction, and his renal function remained normal. There were no other signs of an agglutinin reaction in the postoperative period. He was discharged home on postoperative day 15, with his hospitalization prolonged by paroxysmal atrial fibrillation, which had also been a problem preoperatively.

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Comment

The primary cold autoimmune diseases include cold hemagglutinin disease, paroxysmal cold hemoglobinuria, and cryoglobulinemia. This uncommon group of immunologic disorders is characterized by the abnormal production of autoantibodies, usually of the immunoglobulin M class but occasionally of the immunoglobulin G and immunoglobulin A classes. They are directed against the I antigen or related antigens on erythrocytes of autologous blood. Cold agglutinins have a range of thermally mediated immunologic activity referred to as the thermal amplitude. Below this temperature antigen-antibody complexes form, resulting in hemagglutination, hemolysis, or precipitation from solution [1].

A variety of cold-mediated problems have been encountered during cardiac operations in patients with cold autoimmune disease. Systemic hypothermia during cardiac operations may be associated with massive hemagglutination, widespread microvascular thrombosis, immediate or delayed hemolysis, and immune complex or hemolytic nephritis causing acute or chronic renal failure. Coronary perfusion with cold blood or iced potassium cardioplegic solutions may cause intracoronary hemagglutination with coronary thrombosis, subendocardial ischemia, and, possibly, myocardial infarction.

Several methods have been employed to avoid these detrimental effects of hypothermia in both the systemic and intracoronary circulations. Preoperative plasmapheresis has been used to temporarily reduce cold agglutinin titers [2]. Also described is a combination of mild systemic

hypothermia and coronary washout with normothermic cardioplegia during aortic cross-clamping, immediately followed by hypothermic cardioplegia [3, 4]. Finally, the combination of systemic normothermia and continuous coronary perfusion of a fibrillating heart without aortic cross-clamping has been proposed as an effective method of dealing with this disorder [1].

The use of warm cardiac surgery as described by Lichtenstein and associates [5] avoids the problems associated with cold autoimmune disease because the patients are not exposed to the precipitating factor, hypothermia. Our case illustrates the successful use of this technique in a patient with cryoglobulinemia, but patients with other cold autoimmune diseases may likewise benefit.

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Use of a Heat Exchanger to Prevent Hypothermia During Thoracic and Thoracoabdominal Aneurysm Repairs

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Hypothermia is a common unplanned occurrence in many patients undergoing repair of thoracic and thoracoabdominal aneurysms. Many undesirable side effects of hypothermia have been documented, including decreased cardiac output, conduction abnormalities, and blood coagulopathies. We have developed a simple system that incorporates a Sci-Med Biotherm heat exchanger into our left heart bypass circuit. This provides us with the ability to actively rewarm the patient safely and

efficiently. This study looks at 16 consecutive patients undergoing repair of thoracic or thoracoabdominal aneurysms. In the 9 patients in whom the heat exchanger was used, there were no adverse effects related to the heat exchanger. All patients had significantly higher temperatures at the conclusion of the procedure than the 7 patients in whom the heat exchanger was not used.

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In 1984, the Bio-Medicus centrifugal pump was first reported as a useful adjunct in the repair of traumatic rupture of the aorta [1]. Since that time, left heart bypass with the use of the Bio-Medicus pump has been widely used during the repair of descending thoracic and thoracoabdominal aneurysms [2-4]. During this same period, somatosensory evoked potentials [5], cerebrospinal fluid pressure monitoring [6], upper and lower extremity pressure monitoring, and Swan-Ganz catheters to measure cardiac filling pressures and cardiac output during the procedure are now also used at most centers. The placement of these sophisticated monitoring catheters takes time; although heating blankets have been used, the patients' temperatures often drop before the actual incision is made. In addition, the operation may require a thoracoabdominal incision, which also results in heat loss [7]. Although blood warming devices and heating blankets are used these have been ineffective in consistently maintaining patients' normal temperature. Because of our concern over the decreased cardiac output [8], conduction abnormalities [9], arrhythmias, and coagulopathies [10] that are associated with serious hypothermia, we thought that the ability to maintain or rewarm a patient during left heart bypass would be a useful adjunct to the procedure.

This report describes our technique in 16 consecutive patients undergoing repair of thoracic or thoracoabdominal aneurysms with or without the use of a heat exchanger (Table 1).

Technique

After patients are placed on the operating table, a right heart catheter is passed through the right internal jugular vein to monitor cardiac output and pulmonary capillary wedge pressure. Arterial pressure monitoring catheters are then placed in the right radial and right dorsalis pedis vessels for upper and lower extremity pressure monitoring. When anesthesia has been induced, a double-lumen endotracheal tube is placed and positioned appropriately. Somatosensory evoked potential monitoring is done routinely, and the appropriate electrodes are positioned. Cerebrospinal fluid pressure monitoring is accomplished with lumbar puncture.

A standard left posterior lateral thoracotomy or thoracoabdominal incision is then made, and the left common femoral artery is isolated for perfusion, as is the left atrial appendage. The Sci-Med Biotherm heat exchanger (Sci-Med Life Systems, Minneapolis, MN) is incorporated into our standard tubing pack, which is a Carmeda-coated left heart bypass system (Medtronic Blood Systems, Anaheim, CA) using a BioMedicus centrifugal pump (Medtronic Blood Systems) (Fig 1). The system is primed by gravity using sterile technique, ensuring that it is bubble-free. Varying sizes of wire-reinforced Carmeda-coated perfusion cannulas (Research Medical, Salt Lake City, UT; and Medtronic Blood Systems) are used depending on the atrial size. For distal aortic perfusion or femoral artery perfusion, varying sizes of Carmeda-coated arterial cannulas are used as well; the prime is 500 mL.

Before bypass, the patients are heparinized with 5,000 units of heparin to obtain an activated clotting time of approximately 180 seconds. Flows generally range between 3 and 4 L/min, and distal perfusion pressure is

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Table 1. Preoperative Data in Patients Undergoing Repair of Thoracic or Thoracoabdominal Aneurysms With (Group 1) and Without (Group 2) Use of a Heat Exchanger

Variable	Group 1	Group 2
No. of patients	9	7
Age (y)	55.8 ± 6.8	45.6 ± 7.7 ^a
Sex (M/F)	6/3	6/1
Thoracoabdominal aneurysm repair	7	2
Thoracic aneurysm repair	2	5

^a Not significantly different from group 1.

maintained between 50 and 60 mm Hg. Cerebrospinal fluid pressure monitoring is accomplished in an attempt to maintain the pressure between 10 and 15 cm H₂O. Body temperature is monitored by placement of a Foley catheter with a thermistor probe. Temperature measurements were made on all 16 patients when they entered the room, before bypass, at the end of bypass, and postoperatively (Table 2). We set the water bath temperature at 34°C while the surgical repair was being completed. This was done to possibly add additional spinal cord protection. The temperature, however, was not allowed to go to less than 31°C because of the potential for cardiac irritability.

At the conclusion of the arterial repair we begin to actively rewarm the patient. Bypass is discontinued when the bladder temperature reaches 37.4° ± 0.2°C, and the appropriate dose of protamine is administered. Blood from the circuit is then aspirated into a Cell Saver (Haemonetics, Braintree, MA) device, processed, and returned to the patient. This technique has been used in 9 consecutive patients undergoing thoracic or thoracoabdominal aneurysm repair. We have retrospectively compared these patients with 7 patients who underwent repair without a heat exchanger (see Table 1).

Results

The outcome and complications for these 16 patients are detailed in Tables 3 and 4. No patient died within 30 days of operation. There are 2 patients who died during their period of hospitalization. Both of these patients were in group 1, in which the heat exchanger was used. These 2 patients had undergone repair of complex thoracoabdominal aneurysms. These were the only patients in whom renal failure, ischemic bowel, hepatic failure, and sepsis developed, all of which occurred late in their postoperative course. One patient in this group required reexploration for bleeding. The bleeding vessel was controlled at the time of reoperation.

In the patients without the heat exchanger, there was only one major complication. Paresis of the lower extremities developed in this patient. There were no neurologic complications in those patients with the heat exchanger. There were no serious intraoperative arrhythmias in either group.

We also looked at blood product use in the two groups.

Patient populations were not similar, however. Group 1 had a large percentage of elective thoracoabdominal repairs (7 of 9 patients), whereas group 2 tended to be patients undergoing emergency repair of thoracic aneurysms (5 of 7 patients). Table 4 illustrates perioperative blood product use and postoperative losses in our patients. The numbers are too small and the groups too diverse to make statistical comparisons.

We did, however, closely evaluate the effectiveness of the heat exchanger in terms of rewarming the patients. Table 2 illustrates the temperatures in our patients. In those patients in whom the heat exchanger was used, the temperature was lowered to 34.1° ± 0.2°C on bypass, and all patients were rewarmed to 37.4° ± 0.2°C before bypass was completed. These patients maintained their temperature before transfer to the surgical intensive care unit. In contrast, the temperatures of patients in whom the heat exchanger was not used tended to drift down to 35.8° ± 0.2°C before bypass, drop an average of 0.9° ± 0.2°C during bypass, and remain significantly lower before transfer to the surgical intensive care unit (35.1° ± 0.3°C). This has illustrated to us the effectiveness of the Sci-Med heat exchanger in preventing hypothermia during the repair of thoracic and thoracoabdominal aneurysms.

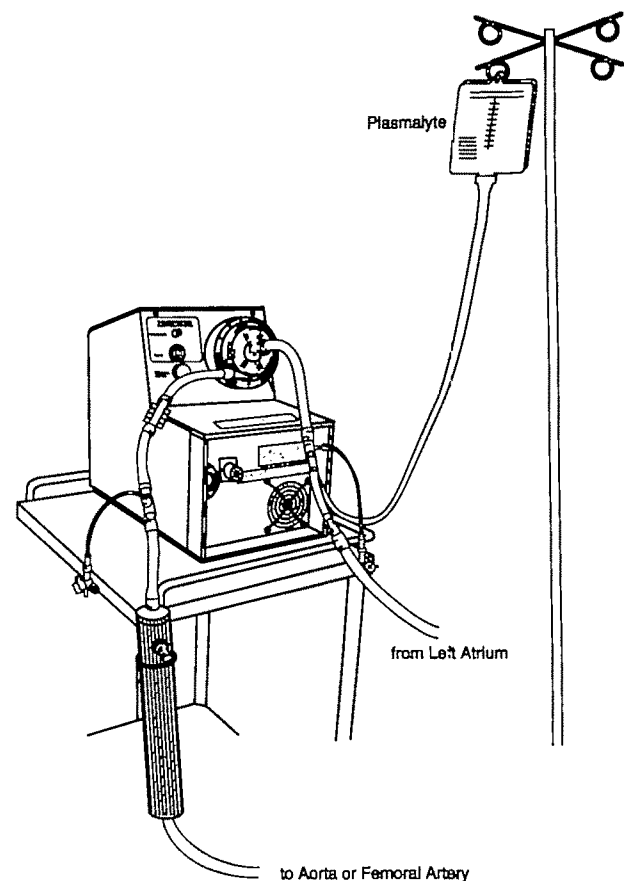


Fig 1. Perfusion system incorporating a SciMed Biotherm and Bio-Medicus centrifugal pump.

Table 2. Comparison of Temperatures During Repair of Thoracic or Thoracoabdominal Aneurysms With (Group 1) or Without (Group 2) Use of a Heat Exchanger^a

Group	Preop	Before Bypass	Bypass	After Bypass	Postop
1	35.7 ± 0.1	34.4 ± 0.2	34.1 ± 0.2	37.4 ± 0.2 ^b	36.7 ± 0.1
2	36.6 ± 0.3	35.8 ± 0.2	34.9 ± 0.4	34.9 ± 0.2 ^c	35.1 ± 0.3 ^d

^a All values are in degrees Celsius. ^b $p < 0.05$ compared with bypass temperature. ^c $p < 0.05$ compared with group 1 after bypass. ^d $p < 0.05$ compared with group 1 postop.

Comment

Hypothermia, defined as a core temperature less than 36°C, is an everyday unplanned occurrence in most operating rooms [7]. Many factors precipitate hypothermia. They include cold ambient operating room temperatures, general anesthesia with central nervous system depression, decreased metabolic rate and vasodilatation, exposed sedated patients, and surgical procedures requiring large open exposures [7]. Trauma patients with traumatic tear of the aorta are especially prone to hypothermia. In these patients, the time required to extricate, transport, and work-up the patient all lead to varying degrees of cooling. In addition, these patients often receive large volumes of resuscitative fluids that are not prewarmed. Therefore hypothermia, before entering the operating room, can be quite severe.

In our series of patients, the temperature before institution of left heart bypass averaged $34.2^\circ \pm 0.3^\circ\text{C}$. After bypass the two groups showed a significant difference in temperature before the completion of the operation. Hypothermia affects each organ system differently. The cardiovascular system begins to show changes at 32°C with a decrease in cardiac output [8]. At 30°C the cardiac output is 40% of normal and sinus bradycardia is seen. Conduction abnormalities also begin to appear at this particular temperature. Ventricular fibrillation is common as the temperature approaches 28°C, especially in the presence of an ischemic myocardium or in patients with

coronary artery disease [9]. We did not see serious intra-operative arrhythmias in our patients, possibly because the temperature in both groups was not less than 34°C.

The blood's coagulation processes are enzymatic reactions that are dependent on temperature. Ferrara and associates [10] demonstrated in their review of 45 trauma patients requiring massive transfusion that patients with a core temperature less than 34°C had a statistically significant increase in coagulopathy and mortality. This occurred despite adequate blood, plasma and platelet administration. They felt the avoidance or correction of hypothermia seemed to be the most important factor in preventing or correcting these coagulopathies.

Others have shown that hypothermia at 32°C results in

Table 3. Outcome in Patients Undergoing Thoracic or Thoracoabdominal Aneurysm Resection With (Group 1) and Without (Group 2) Use of a Heat Exchanger

Variable	Survivors		Nonsurvivors	
	Group 1	Group 2	Group 1	Group 2
No. of patients	7	7	2 ^a	0
Operative death (<30 d)	...	...	0	0
Hospital death (>30 d)	...	...	2	0
Complications				
Renal failure	0	0	2	0
Ischemic bowel	0	0	1	0
Sepsis	0	0	1	0
Liver failure	0	0	1	0
Lower extremity paresis	0	1	0	0
Reoperation for bleeding	1	0	0	0

^a Both patients underwent complex thoracoabdominal aneurysm repair.

Table 4. Comparison of Blood Product Data in Patients Undergoing Thoracic or Thoracoabdominal Aneurysm Repair With (Group 1) or Without (Group 2) the Use of a Heat Exchanger

Variable	Group 1	Group 2
Thoracic Aneurysm Repair ^a		
Hematocrit		
Preop	0.36 ± 0	0.31 ± 0.01
12 h postop	0.31 ± 0.01	0.27 ± 0.02
Intraop		
PRBC (mL)	500 ± 0	745 ± 318.2
FFP (mL)	250 ± 250	200 ± 122.5
Plt (U)	10 ± 1	4 ± 4
Cryo (U)	0	2 ± 2
Postop (1st 12 h)		
PRBC (U)	0	0.4 ± 0.2
Chest tube output (mL)	400 ± 200	682 ± 250.8
Thoracoabdominal Aneurysm Repair ^b		
Hematocrit		
Preop	0.38 ± 0.01	0.39 ± 0
12 h postop	0.33 ± 0.01	0.34 ± 0
Intraop		
PRBC (mL)	2,407.1 ± 505.6	1,125 ± 375
FFP (mL)	821.4 ± 118.5	1,000 ± 0
Plt (U)	11.4 ± 4	20 ± 0
Cryo (U)	8.0 ± 3.4	5.5 ± 4.5
Postop (1st 12 h)		
PRBC (U)	0.1 ± 0.1	0.5 ± 0.5
Chest tube output (mL)	530 ± 68.1	352.5 ± 102.5

^a Group 1, $n = 2$; group 2, $n = 5$. ^b Group 1, $n = 7$; group 2, $n = 2$.

Cryo = cryoprecipitate; FFP = fresh frozen plasma; Plt = platelets; PRBC = packed red blood cells.

a significant prolongation of partial thromboplastin time, a significant decrease in platelet counts and platelet aggregation, prolonged onset times, and a decreased rate of Sonoclot formation, as well as a shortened euglobulin lysis time [11, 12]. All these changes returned to normal by rewarming, and the changes were most likely due to decreased function of the clotting factors. Hypothermia appears to make the blood hypocoagulable and cause platelet sequestration in the liver and release of plasminogen activators in the fibrinolytic system [11, 12]. Although we could not show significant changes with respect to blood product use in our patients, this is likely secondary to the small numbers of patients and the diversity of our groups.

Hypothermia also leads to peripheral vasoconstriction. This increased afterload can cause significant stress on the myocardium, as well as severe arterial hypertension [9]. This may threaten the integrity of the multiple anastomoses required during thoracoabdominal procedures.

The spinal cord's sensitivity to ischemia is well known and documented [13]. A number of factors may protect the cord during operation. We have used spinal cord evoked potential monitoring to detect serious ischemia. We have also measured cerebrospinal fluid, pressure and we withdraw fluid when necessary. Hypothermia may also have a protective effect on the spinal cord during the period of aortic clamping. For this reason, our patients were kept cold until the clamp was removed. Although the numbers are small, we did not have any patients in this group who suffered any adverse neurologic sequelae.

To reverse the hypothermia that occurs during the repair of thoracic and thoracoabdominal aneurysms, we have incorporated the Sci-Med Biotherm heat exchanger in our Carmeda-coated left heart bypass tubing packings. This has allowed our patients to leave the operating room with a normal temperature. Before we began using this system, patients were routinely hypothermic when they were returned to the surgical intensive care unit. Using this system in 9 consecutive patients, we have seen no adverse reactions.

In conclusion, unplanned hypothermia is a common occurrence in patients undergoing the surgical repair of thoracic and thoracoabdominal aneurysms. Many undesirable side effects of hypothermia have been well documented, all of which can increase the patient's operative

morbidity and potential mortality. Use of the Sci-Med Biotherm heat exchanger, in conjunction with left heart bypass, provides the ability to actively rewarm patients safely and efficiently.

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Selective Jugular Cannulation for Safer Retrograde Cerebral Perfusion

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Hypothermic retrograde cerebral perfusion is a new technique for protecting the brain. Satisfactory cerebral protection should be possible even for periods of retrograde perfusion greater than 60 minutes. However, there are some concerns that functioning venous valves at the jugular-subclavian junction may impede retrograde flow to the brain and consequently cerebral protection may

not be adequate. To overcome this obstacle, we have developed an easy and safe technique of selective jugular cannulation through the right atrium using a central venous catheter and a guidewire. We have employed this technique successfully in 15 patients who underwent operation on the aortic arch.

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Profound hypothermic circulatory arrest has been widely used during aortic arch operations since it was introduced by Griep and associates [1]. Although the maximum duration of circulatory arrest without sequelae has not been clearly defined, neurological damage becomes evident if the ischemic interval exceeds 60 minutes [2]. To overcome this disadvantage, we developed a technique of retrograde total body perfusion through both venae cavae to protect the brain and other systemic organs [3]. We have employed this technique in 34 patients undergoing operations on the aortic arch. Good cerebral protection has been obtained by this method in most patients, including 2 in whom periods of retrograde perfusion exceeded 100 minutes [3]. In first 19 patients retrograde perfusion was performed through conventional caval cannulas, but one of these patients sustained serious neurological damage despite a relatively short duration of retrograde perfusion. Judging from the observation that only her head and neck were completely free of edema just after the operation, it is presumed that a competent valve at the venous angle was impeding retrograde flow through the superior vena cava to the brain. To achieve adequate cerebral protection during retrograde perfusion through the venae cavae, we have developed a new technique that employs a cavoatrial cannula inserted selectively into the internal jugular vein beyond the valve at the venous angle and have applied this technique in the last 15 patients.

Technique

At the induction of anesthesia, a Swan-Ganz catheter and a 7F or 8F central venous catheter are inserted into the

internal jugular vein for pressure monitoring and drug infusion, and the latter is advanced about 20 cm to locate the catheter tip in the right atrium when retrograde perfusion is performed. The operation is performed using cardiopulmonary bypass with bicaval venous cannulation through the right atrium and common femoral arterial cannulation. Total cardiopulmonary bypass is established, and systemic cooling is commenced. The ascending aorta is then cross-clamped and cold blood cardioplegic solution is infused retrogradely through the coronary sinus. After the proximal ascending aorta is opened to assess the inner aortic wall and the aortic valve, proximal aortic repair is performed. The completion of proximal aortic repair usually coincides with the endpoint of core cooling with the rectal temperature reaching less than 20°C. At this point, pump perfusion is temporarily discontinued, the superior vena caval cannula is removed, and both venae cavae are snared. The "reversed over-the-wire catheter cannulation" technique is now described in detail. A short atriotomy is performed in the upper portion of the right atrium, and the tip of a central venous catheter is identified (Fig 1A). A 0.35-inch guidewire 150 cm in length passing in a 24F or 26F venous cannula is inserted into the central venous catheter tip and advanced to the neck in the reverse direction (Fig 1B). Holding and tensing each end of the guidewire both in the operative field and at the anesthesiologist's side, the snare around the superior vena cava is released temporarily and the venous cannula is advanced over the central venous catheter selectively into the internal jugular vein beyond the venous valve at the venous angle (Fig 1C). The position of the cannula tip can be easily confirmed by palpation of the neck by the anesthesiologist if it is located in the internal jugular vein. The guidewire is pulled out by the anesthesiologist, and the venous cannula is connected to the extracorporeal circuit (Fig 1D). Usually the

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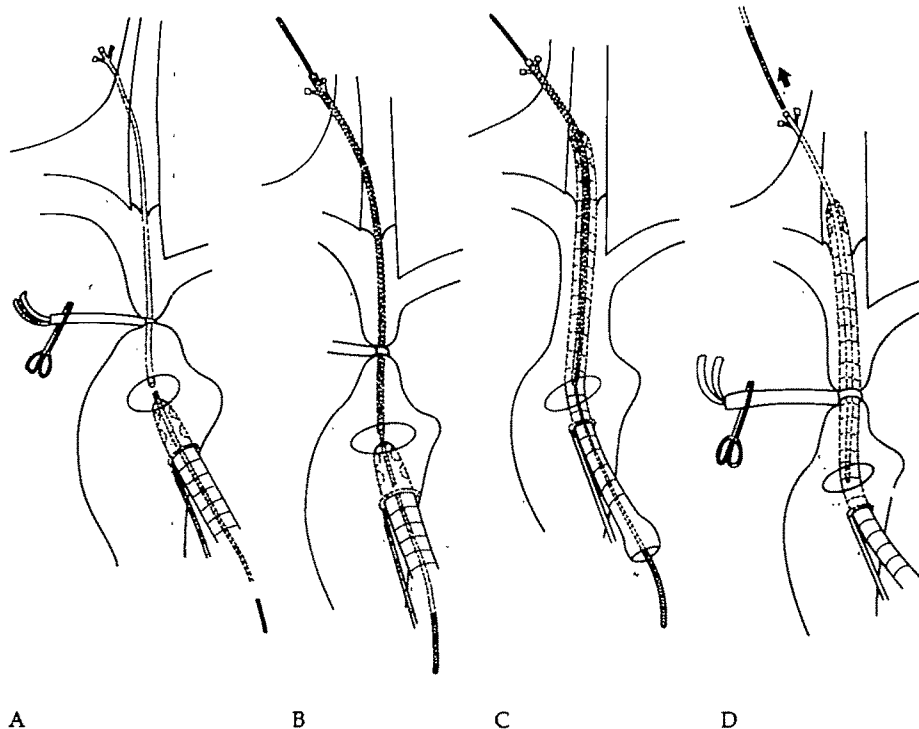


Fig 1. Essential steps for selective jugular cannulation: (A) A 7F or 8F central venous catheter is inserted into the right atrium through the internal jugular vein at the induction of anesthesia. When proximal repair is accomplished and the rectal temperature falls to less than 20°C, pump perfusion is temporarily discontinued and the superior vena caval cannula is removed. A short atriotomy is performed, and a 0.35-inch guidewire 150 cm in length passing in a 24F or 26F venous cannula is inserted into the central venous catheter tip. (B) The guidewire is advanced to the neck in the reverse direction. (C) A venous cannula is advanced over the central venous catheter selectively into the internal jugular vein beyond the venous valve at the venous angle. (D) The guidewire is pulled out by the anesthesiologist, the superior vena caval cannula is connected to the cardiopulmonary bypass circuit, and the central venous catheter is connected to a transducer to monitor the perfusion pressure.

above-mentioned procedures require only a few minutes. The aortic clamp is removed and retrograde perfusion is initiated; open distal anastomosis is then performed (Fig 2).

Comment

Profound hypothermic circulatory arrest makes it unnecessary to apply the aortic clamp and consequently can afford a bloodless operative field and simplifies the operative procedure on the aortic arch. However, many authors agree that the risk of neurologic sequelae becomes significant if the period of the circulatory arrest exceeds 45 to 60 minutes in humans when the nasopharyngeal temperature is 15 to 18°C [1, 2], although a longer time is occasionally required to accomplish distal aortic repairs.

Retrograde perfusion through the superior vena cava was first clinically employed to evacuate air in the systemic circulation during cardiopulmonary bypass by Mills and Ochsner in 1980 [4]. Lemole and associates [5] applied this method to implanting an intraluminal sutureless graft for acute aortic dissection in 1982. Ueda and associates [6] employed this technique to extend the safe duration of hypothermic circulatory arrest during the surgical treatment of the aortic arch aneurysm in earnest. Furthermore, we have developed a technique of continuous retrograde total body perfusion to protect not only the brain through the superior vena cava, but also the abdominal visceral organs through the inferior vena cava [3]. However, there are some concerns that venous valves may impede retrograde flow to the brain and consequently cerebral protection may not be adequate whether the perfusion is performed only through the superior vena cava or through both venae cavae.

Venous valves in the internal jugular vein are present at the venous angle (jugular-subclavian junction) in 80% to 90% of humans. Most of these valves are vestigial and

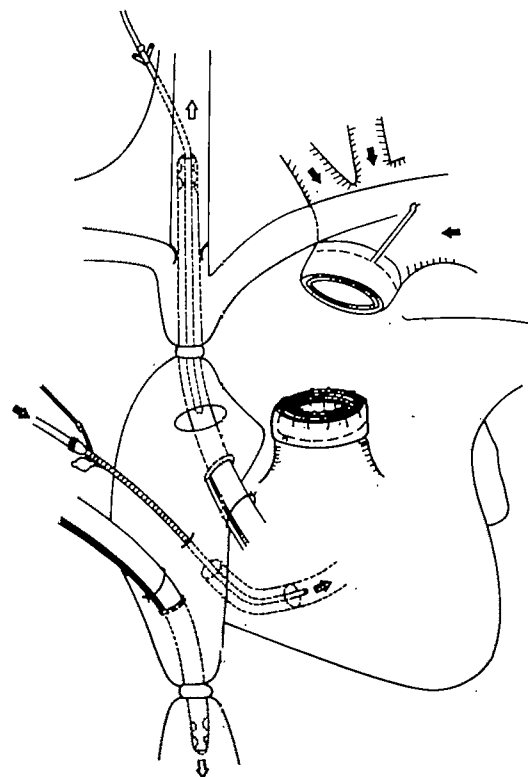


Fig 2. The aortic clamp is removed and retrograde perfusion is initiated; open distal anastomosis is then performed. (○→ oxygenated blood perfusing systemic organs; ■→ deoxygenated blood returning from the body; ▤→ cold blood cardioplegia.)

incompetent, but in some patients (10% to 20%) they are functioning and may interfere with retrograde flow through the superior vena cava to the brain [7]. Because there are no valves in the internal jugular vein above the venous angle as well as in the intracranial sinuses, we believe that the superior vena caval cannula should be placed in the internal jugular vein beyond the venous valves at the venous angle to achieve adequate cerebral protection during hypothermic retrograde perfusion. Although selective cannulation into the internal jugular vein through the right atrium is difficult and could even be traumatic to thin and friable venous walls if it were attempted without a guide, the reversed over-the-wire catheter cannulation technique that we have described here enables selective cannulation to be done easily. This technique has proved to be safe and reproducible in 15 consecutive patients who underwent aortic arch operations since November 1991. This technique may provide more effective cerebral protection than simple retrograde perfusion through the superior vena cava.

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Pericardioperitoneal Window

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A technique to create a pericardial window is discussed. By creating a communication between the pericardial and peritoneal cavities, adequate drainage is obtained without the need for external draining systems. The technique is simple, easy to learn, and without serious complications.

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The subxiphoid approach used to drain pericardial effusions has been described in the medical literature [1-4]. Modifications of this technique have also been presented [5, 6]. Most surgeons prefer this approach to the transthoracic window, because the subxiphoid approach is an easier operation with lower morbidity. The video-assisted thoracoscopic pericardial window, although requiring smaller incisions, still depends on the ability of the patient to sustain one-lung general anesthesia and to be positioned laterally.

The subxiphoid approach is performed through an upper midline incision with the patient in the supine

position under general or local anesthesia. The linea alba is divided, and the pericardium is exposed. After a window is created in the pericardial sac, the fluid is evacuated, and a drainage system is left in place to collect any reaccumulation of fluid. A disadvantage of this procedure is the inconvenience of having a tube inserted in the pericardium that may need to remain in place for several days. This may become uncomfortable for the patients, could prolong the hospital stay, and increases the chances of infection in the pericardial cavity through an open incision. A simple modification of this technique was described by Dabir and Warren in 1984 [7]. We believe it is a safe and useful method to drain pericardial effusions.

Technique

After the pericardial sac is exposed and the fluid is evacuated, the diaphragmatic surface of the pericardium is visualized, and an opening is created to join the pericardial and peritoneal cavities (Fig 1). The window is at least 2 × 2 cm; the cut edges of the pericardium,

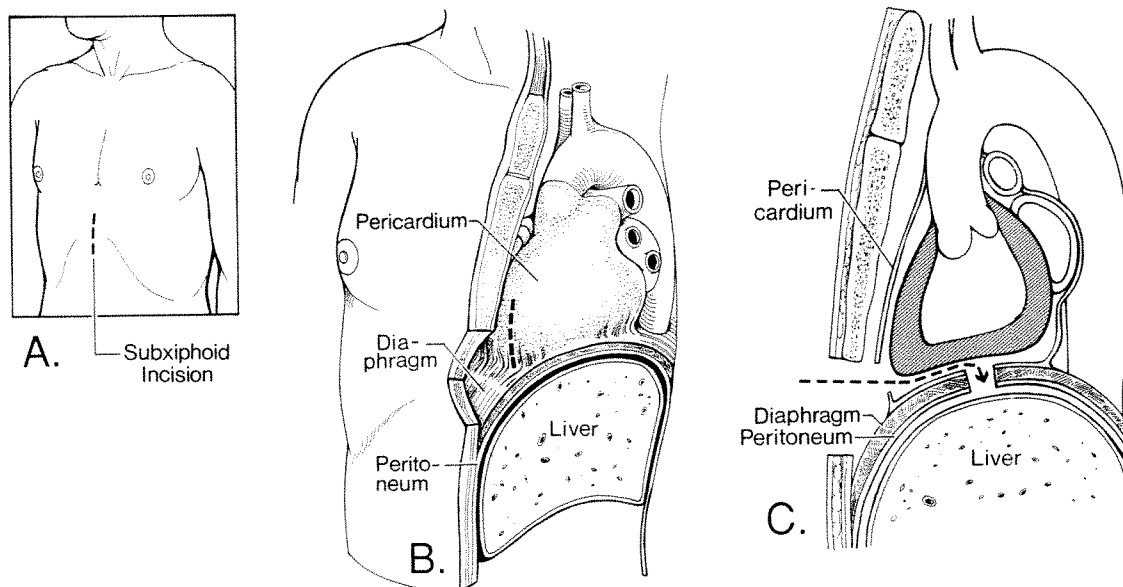


Fig 1. (A) Insert showing the vertical subxiphoid incision. (B) The juxtaposition of the pericardial and peritoneal cavities is emphasized. The pericardium is opened through a vertical incision. (C) After the window is created, interrupted sutures are placed to hold all layers together and to ensure patency.

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diaphragm, and peritoneum are sutured together with a few interrupted sutures. The dome of the liver prevents any abdominal viscera from herniating into the pericardial cavity, and the subdiaphragmatic recess acts as a collection chamber for the pericardial fluid. No external drains are necessary, and the linea alba, subcutaneous tissues, and skin are closed in the usual manner. Patients can be discharged as soon as their condition permits.

Comment

We have used this approach in 15 patients. Of these, 12 had a diagnosis of malignancy, and metastatic disease to the pericardium was suspected. The other 3 patients had effusions of undetermined cause. Because all cultures were negative, the effusions were classified as idiopathic. This simple modification is useful in the management of noninfectious pericardial effusions; adequate drainage was obtained, and no serious complications occurred related to the procedure.

In uremic pericardial effusions, it may be inadvisable to

create this communication in patients undergoing peritoneal dialysis.

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Preparation of Autologous Fibrin Glue From Pericardial Blood

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To salvage patients' blood and improve hemostasis in cardiac operations, autologous fibrin glue was prepared in a new way by means of ethanol from pericardial blood. The yield from 44 mL of blood was 2.1 ± 0.7 mL (mean $\pm$ standard deviation) of fibrinogen concentrate with a concentration of 25.1 ± 7.5 mg/mL; 2.7 mL of

two-component glue was obtained after the addition of thrombin solution. The glue has the advantages of safety from transmission of viral diseases and from immunologic reactions.

(*Ann Thorac Surg* 1993;55:543-4)

Hemostasis and salvage of patients' blood is crucial in modern operations to avoid blood transfusion. Autologous fibrin glue is a hemostatic agent that can be prepared by means of ethanol [1-3]. To salvage patients' blood and improve hemostasis in cardiac operations, this study was designed to test the possible preparation of autologous fibrin glue from pericardial and mediastinal blood.

Patients and Methods

Twenty-eight patients admitted for elective coronary artery bypass grafting were included in this study. The 24 men and 4 women participating had a mean age of 61 years (range, 30 to 71 years), a mean weight of 77.9 kg (range, 46 to 108 kg), and a mean hemoglobin level of 8.8 g/L (range, 7.3 to 10.1 g/L).

After sternotomy but before the pump suction could be used, 44 mL of pericardial and mediastinal blood was drawn into a syringe containing 6 mL of heparin (20 IU/mL) and citrate (129 mmol/L) as anticoagulant. The plasma was separated from the blood cells by centrifugation, and the fibrinogen was precipitated with ethanol (99%) by incubation at 0°C for one-half hour. The preparation was completed in a closed system to ensure sterility [1-3]. The fibrinogen concentration in the concentrated solution was measured by the method described by Weis-Fogh [1]. The second component of the glue contained thrombin, 1,200 IU/mL, calcium chloride, 100 mmol/L, and aprotinin, 6,000 KIU/mL.

Results

The mean volume of fibrinogen concentrate was 2.1 ± 0.7 mL (mean $\pm$ standard deviation) with a concentration of 25.1 ± 7.5 mg/mL. After 0.3 parts of thrombin solution was added, the total volume of two-component fibrin glue

was 2.7 mL. The glue was sterile and could be prepared in less than 90 minutes.

Comment

A small volume of blood is wasted during opening and cannulation in cardiac operations before the pump suction can be used. In this study we were able to collect the blood from the pericardium and the mediastinum in a syringe containing anticoagulant, and to prepare fibrinogen concentrate from the blood. The outcome was a good yield of fibrin glue comparable with autologous glue prepared from venous blood by the same method (fibrinogen concentration, 28 mg/mL) [2, 3]. Autologous fibrin glue can be prepared in different ways [4-7]. Experimental data suggest that the glue's strength is related to the fibrinogen concentration [8]. Autologous fibrin glue prepared by means of ethanol is suitable for clinical use as a hemostatic agent and as a sealant of pulmonary air leak and of high-porosity vascular prostheses [2, 3]. Additionally it has the advantages of safety from transmission of viral diseases and immunologic reactions [1-3, 9]. Currently we are testing a new device with which sterile fibrinogen concentrate can be prepared in less than 30 minutes, making it more useful in acute operations.

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Notice From the American Board of Thoracic Surgery

The American Board of Thoracic Surgery began its recertification process in 1984. Diplomates interested in participating in this examination should maintain a documented list of the operations they performed during the year prior to application for recertification. This practice review should consist of 1 year's consecutive major operative experiences. (If more than 100 cases occur in 1 year, only 100 need to be listed.) They should also keep a record of their attendance at approved postgraduate medical education activities for the 2 years prior to application. A minimum of 100 hours of approved CME activity is required.

In place of a cognitive examination, candidates for recertification will be required to complete both the general thoracic and cardiac portions of the SESATS IV syllabus (Self-Education/Self-Assessment in Thoracic Surgery). It is not necessary for candidates to purchase

SESATS IV booklets prior to applying for recertification. SESATS IV booklets will be forwarded to candidates after their applications have been accepted.

Diplomates whose 10-year certificates will expire in 1995 may begin the recertification process in 1993. This new certificate will be dated 10 years from the time of expiration of the original certificate. Recertification is also open to any diplomate with an unlimited certificate and will in no way affect the validity of the original certificate.

The deadline for submission of applications is May 1, 1993. A recertification brochure outlining the rules and requirements for recertification in thoracic surgery is available upon request from the American Board of Thoracic Surgery, One Rotary Center, Suite 803, Evanston, IL 60201.

Sinus of Valsalva Aneurysms and Application of Surgical Science to Their Repair

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Congenital aneurysms located in the sinuses of Valsalva typically expand and may eventually rupture into the right atrium or ventricle. In 1957, Dr Lillehei and colleagues reported 3 patients who underwent successful repair of ruptured sinus of Valsalva aneurysms at the University of Minnesota. This achievement required an accurate understanding of the pathology and anatomy of

sinus of Valsalva aneurysms, as well as the successful application of surgical science to solve the problems posed by the repair of these aneurysms. Doctor Lillehei's article is a classic in the field of cardiothoracic surgery and is now reviewed 36 years after its publication.

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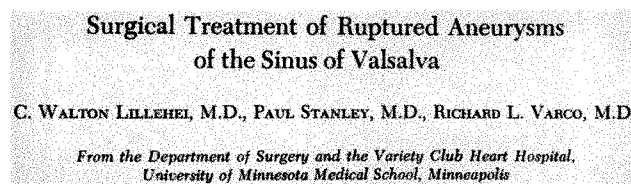


Fig 1. Doctor Lillehei and colleagues published their case reports in *The Annals of Surgery* in 1957 under this title head. (Reprinted from *Ann Surg* 1957;146:459-72, by permission.)

In May 1957, Dr Lillehei and colleagues at the University of Minnesota presented 3 patients who had successful repair of ruptured sinus of Valsalva aneurysms to the annual meeting of the American Surgical Association. The article describing this experience (Fig 1) summarizes knowledge that was gained from observations of human pathology as well as experiments carried out in animals. The article is remarkable both for the quality and originality of its information, and merits review as a reminder of what can be accomplished by the application of surgical science to the solution of clinical problems.

Pathology of Ruptured Sinus of Valsalva Aneurysms

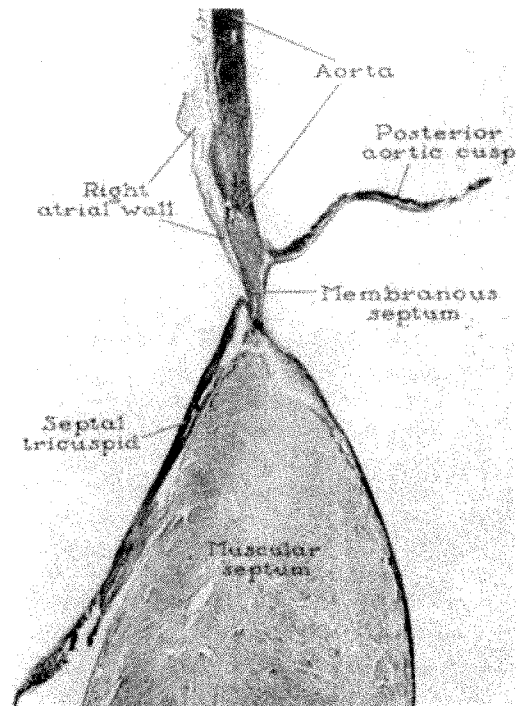
Although reports of sinus of Valsalva aneurysms published in the nineteenth century correctly described the relationship of the aneurysm sac to the right atrium and ventricle, they did not attempt to classify sinus of Valsalva aneurysms according to anatomic location, nor did they discern their congenital etiology. Maude Abbott first postulated that a congenital weakness of the aorta was the cause of sinus of Valsalva aneurysms in a series of observations published in 1919 [1]. In 1957, Edwards and Burchell [2] published photomicrographs (Fig 2) graphi-

cally confirming the deficiency of elastic and muscular tissue immediately above the annulus of the aortic valve that leads to the development of sinus of Valsalva aneurysms. Abbott [1] attributed sinus of Valsalva aneurysms to a developmental deficiency of the distal bulbar septum. This notion is supported by the frequent (30% to 60%) coexistence of ventricular septal defects and sinus of Valsalva aneurysms [3-5]. Moreover, the frequency of these aneurysms is highest in the right sinus of Valsalva, which abuts the largest region of the septum, although aneurysms have been reported to arise from all three sinuses.

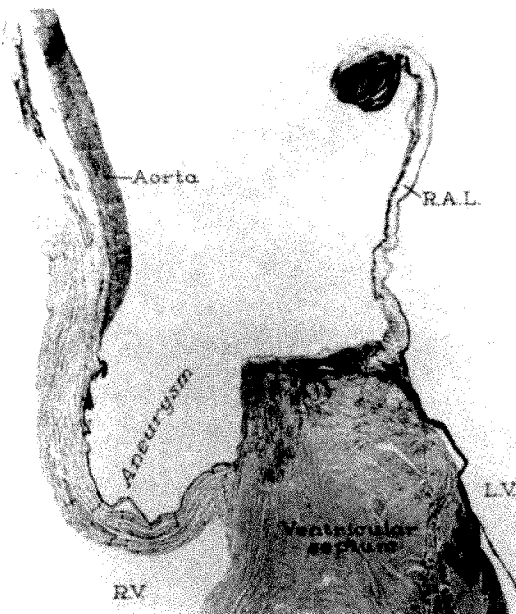
The relationship of the aortic root and sinus of Valsalva aneurysms to the cardiac chambers was beautifully illustrated in the 1949 article of Jones and Langley [6] (Fig 3). Jones and Langley described the possible paths of aneurysm expansion into the right heart; however, the classification system of Sakakibara and Konno [7] is the one most commonly used today to describe the location of sinus of Valsalva aneurysms. According to the nomenclature of Sakakibara and Konno, congenital sinus of Valsalva aneurysms types I through IV are defined according to the position of the aneurysm sac relative to the right or noncoronary aortic valve cusps. This position also determines which cardiac chamber (right atrium or right ventricle) is invaded by the expanding aneurysm.

An expanding sinus of Valsalva aneurysm may take on the appearance of a windsock (Fig 4), although this is not always the case. The fistulous communication that exists between the aorta and the right heart after rupture of a sinus of Valsalva aneurysm can produce acute symptoms of pain and dyspnea; however, 50% to 70% of patients experience slowly progressive symptoms or no symptoms [3-5]. An expanding but unruptured sinus of Valsalva aneurysm can also produce symptoms by obstruction (eg, right ventricular outflow tract obstruction), deformation (eg, left or right coronary ostial deformation with resultant myocardial ischemia) [8], or compression (eg, ventricular tachycardia due to compression of the ventricular septum) [9].

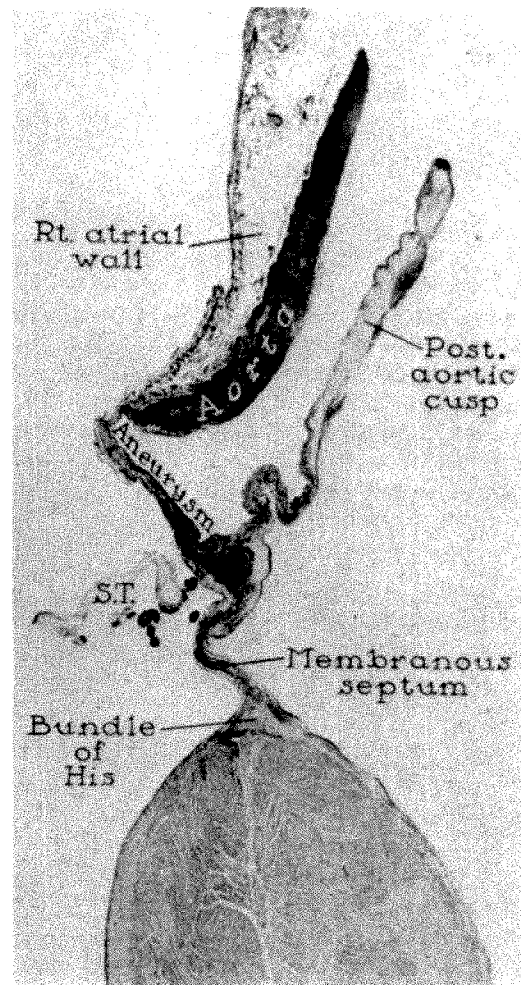
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A



B



C

Fig 2. (A) Longitudinal section of a normal heart taken through the noncoronary sinus of Valsalva. (B) Longitudinal section of the heart demonstrating an aneurysm of the right sinus of Valsalva. (L.V. = left ventricle; R.A.L. = right aortic valve leaflet; R.V. = right ventricle). (C) Longitudinal section of the heart demonstrating a thin-walled sinus of Valsalva aneurysm protruding into the right atrium immediately above the tricuspid valve (Post. aortic cusp = posterior [noncoronary] aortic valve cusp; S.T. = septal leaflet of tricuspid valve). (Reprinted from Edwards JE, Burchell HB. The pathologic anatomy of deficiencies between the aortic root and the heart, including aortic sinus aneurysms. *Thorax* 1957;12:125-39, by permission.)

When a sinus of Valsalva aneurysm ruptures into the right atrium or right ventricle, a harsh continuous murmur is produced. As first outlined by Morch and Greenwood [10] this murmur must be differentiated from the murmurs of a patent ductus arteriosus, ventricular septal defect with associated aortic insufficiency, aortopulmonary window, coronary arteriovenous malformation, or pulmonary arteriovenous malformation. With echocardi-

ography and angiography the diagnosis is easily confirmed except in instances where a sinus of Valsalva aneurysm sac obstructs flow through a subjacent ventricular septal defect and thereby impedes visualization of the septal defect. The fact that 30% to 60% of sinus of Valsalva aneurysms are associated with ventricular septal defects emphasizes the importance of visually confirming ventricular septal integrity at the time of surgical repair.

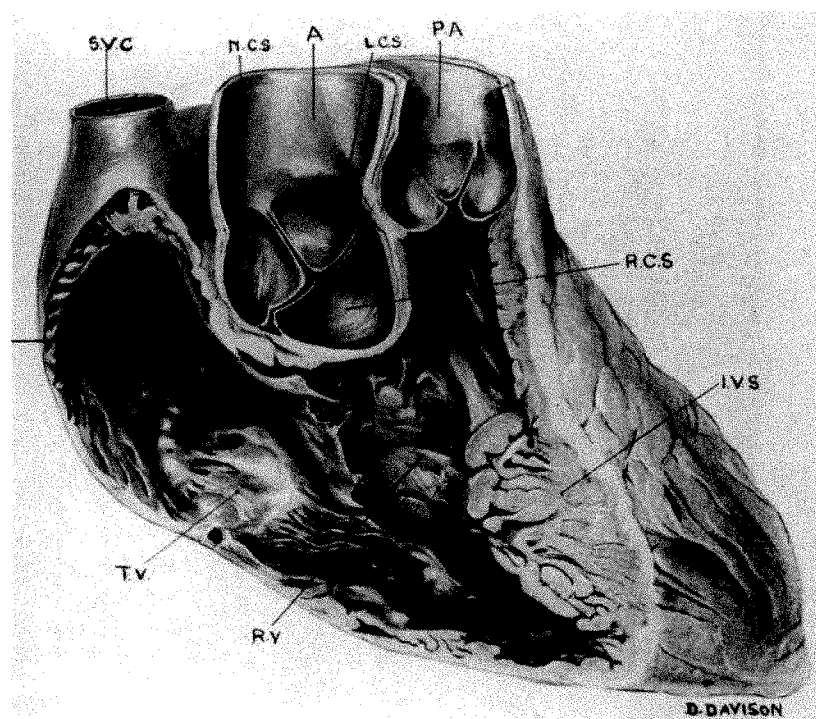


Fig 3. This drawing illustrates the relationship of the sinuses of Valsalva to the structures of the right side of the heart. In their article, Jones and Langley demonstrated an understanding of the anatomy relevant to sinus of Valsalva aneurysms but did not develop a specific classification system. (A = aorta; I.V.S. = interventricular septum; L.C.S. = left coronary sinus; N.C.S. = noncoronary sinus; P.A. = pulmonary artery; R.A. = right atrium; R.C.S. = right coronary sinus; R.V. = right ventricle; S.V.C. = superior vena cava; T.V. = tricuspid valve.) (Reprinted from Jones AM, Langley FA. Aortic sinus aneurysms. *Br Heart J* 1949;11:325-41, by permission.)

Surgical Technique

Before the development of devices and techniques for extracorporeal support, ingenious methods were devised for the closure of ruptured sinus of Valsalva aneurysms using hypothermia and inflow occlusion [11, 12]. The method developed by Morrow and colleagues [11] employed a compressed polyvinyl plug that was passed into the aorta then guided through the mouth of the aneurysm to occlude its orifice. Bigelow's method [12] used hypothermia to 29°C and inflow occlusion to allow suture closure of the aneurysm under direct vision through a right ventriculotomy.

In the cases published by Dr Lillehei and associates, a pump-oxygenator was used to temporarily provide cardiopulmonary function. This oxygenator was a bubble-type device that had been developed and tested in laboratory animal studies by Drs Lillehei, DeWall, Read, Warden, and Varco [13]. It consisted of a vertical blood-oxygen mixing tube that emptied into a spiral settling (ie, defoaming) tube. The oxygenated and defoamed blood then passed into a reservoir from which it was pumped into the patient's arterial system (Fig 5).

In the 3 cases of Dr Lillehei, the ascending aorta was clamped during cardiopulmonary bypass and the sinus of Valsalva aneurysm was repaired (Fig 6). While the repair was accomplished in the first case, retrograde perfusion of the heart using techniques developed in the laboratory [14] maintained myocardial blood flow. Although the technique of retrograde perfusion of the heart had been previously described by other investigators [15], the studies performed by Dr Lillehei's group determined myocardial oxygen consumption and transmyocardial lactate gradients during retrograde perfusion, and critically ex-

amined blood flow distribution to the right and left ventricles. These experiments defined levels of coronary venous pressure and flow that were tolerated by the venous system and still provided adequate temporary support for myocardial metabolism. In a separate prescient study [16] normothermic continuous retroperfusion of hyperkalemic blood was proposed as a method for producing asystole and reducing myocardial oxygen consumption, although this modification of the retroperfusion technique was not used in the patients who had sinus of Valsalva repair.

The second and third patients had cardiac asystole induced by the injection of hyperkalemic blood (2.5% potassium citrate diluted in oxygenator blood) into the coronary circulation. Repair of the aneurysm was then accomplished in the arrested, nonperfused heart. The periods of cardiopulmonary bypass for these three operations were 23, 10, and 17 minutes. None of the patients in Dr Lillehei's report had associated congenital cardiac defects and none had aortic valve insufficiency.

When a ventricular septal defect is associated with a sinus of Valsalva aneurysm, repair of both fenestrations can be made with a single patch if the septal defect is subjacent to the aneurysm [17]. If the septal defect is in a location other than directly subjacent to the aneurysm, then the defects should be repaired separately. It is possible to repair a ventricular septal defect subjacent to a sinus of Valsalva aneurysm through a transaortic exposure; however, this places the specialized conduction system at higher risk for injury than closure of the ventricular septal defect through a right-sided exposure.

Aortic valve replacement with one of the usual prosthetic devices is used to treat severe aortic insufficiency associated with a sinus of Valsalva aneurysm. For less

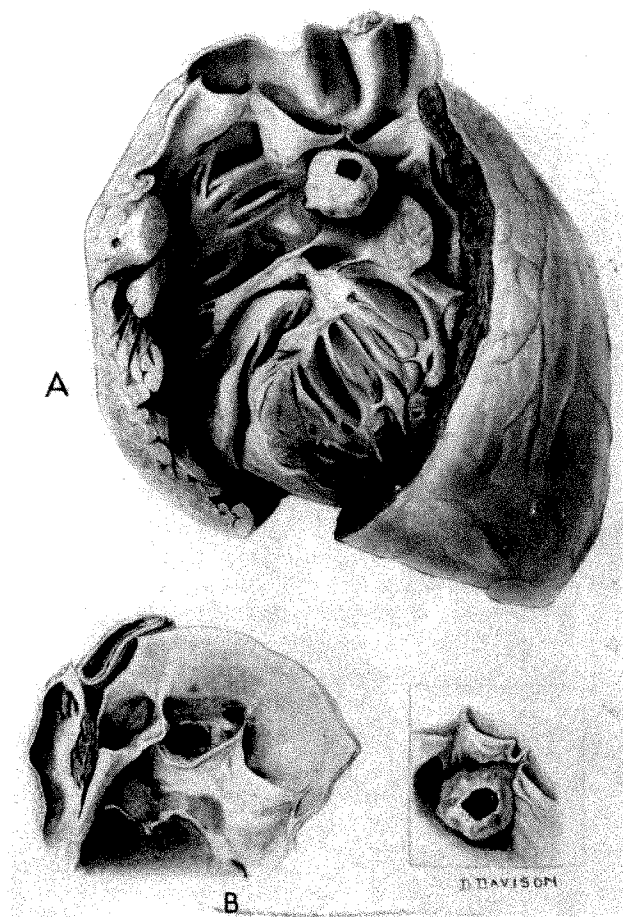


Fig 4. (A) Gross appearance of a ruptured sinus of Valsalva aneurysm. (B) Transaortic view of a ruptured sinus of Valsalva aneurysm. The insert is a detailed view of a ruptured sinus of Valsalva aneurysm. (Reprinted from Jones AM, Langley FA. Aortic sinus aneurysms. *Br Heart J* 1949;11:325-41, by permission.)

severe aortic insufficiency repair of the aortic valve as described by Trusler and associates [18] may be used. In this operation, the aortic valve and annulus are carefully inspected, special attention being paid to the prolapsing cusp responsible for valvular incompetence. After completion of closure of the sinus of Valsalva aneurysm and associated ventricular septal defect (if present), the prolapsing valve leaflet is brought into proper alignment with the other leaflets. At this point the surgeon must judge the amount of excess leaflet tissue and decide if plication of the leaflet at the level of the commissure will restore aortic valve competency (Fig 7). The plicating sutures are reinforced with small pledgets and are taken through the wall of the aorta.

Surgical Outcome

All of the patients in Dr Lillehei's group survived operation. The duration of follow-up was not specified; however, all patients were described as doing well and as experiencing distinct improvements in health after closure of their aneurysms. The postrepair changes in systemic

blood pressure and heart size were documented by pressure tracings and chest roentgenograms.

In his closing remarks, Dr Lillehei stated that "... in this condition the aortic valves are usually normal, so that the surgery can be completely corrective" [19]. This remark was subsequently validated by the experience of other surgeons. The early mortality after repair of congenital sinus of Valsalva aneurysms ranges from 0% to 12% in reported series [3-5, 20] and is primarily related to coexisting cardiac malformations and ventricular dysfunction due to chronic aortic insufficiency. Interestingly, the incidence of severe pulmonary hypertension is low despite the association of sinus of Valsalva aneurysms and ventricular septal defects. This finding may be related to the obstruction to shunt flow posed by the aneurysm sac [20].

Longer term results of sinus of Valsalva aneurysm repair have been reported by several groups [3-5, 21-24]. Recurrence of the aneurysm is rare. In one unusual case, recurrent rupture of a sinus of Valsalva aneurysm was reported 30 years after repair with a polyvinyl plug [25]. The vast majority of patients have persistent improvements in functional class, and late morbidity is most commonly due to recurrence of a previously repaired

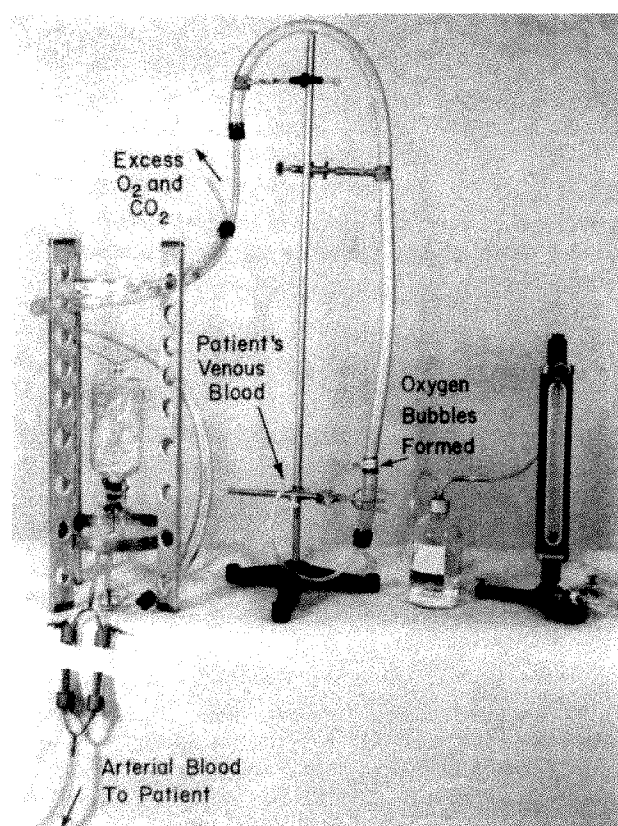


Fig 5. The original bubble oxygenating device developed at the University of Minnesota is illustrated. This oxygenator was made from inexpensive disposable components and was the forerunner of the single-component disposable bubble oxygenating devices. (Reprinted from Lillehei CW, DeWall RA, Reed R, Warden HE, Varco RL. Direct vision intracardiac surgery in man using a simple, disposable artificial oxygenator. *Dis Chest* 1956;29:1-8, by permission.)

ventricular septal defect, native valve endocarditis, or complications associated with a prosthetic or repaired aortic valve.

As described in the previous section, the management of aortic insufficiency coexisting with a sinus of Valsalva aneurysm requires judgements regarding severity of valvular insufficiency and extent of cusp and annular morphologic deformation. Mild degrees of insufficiency may

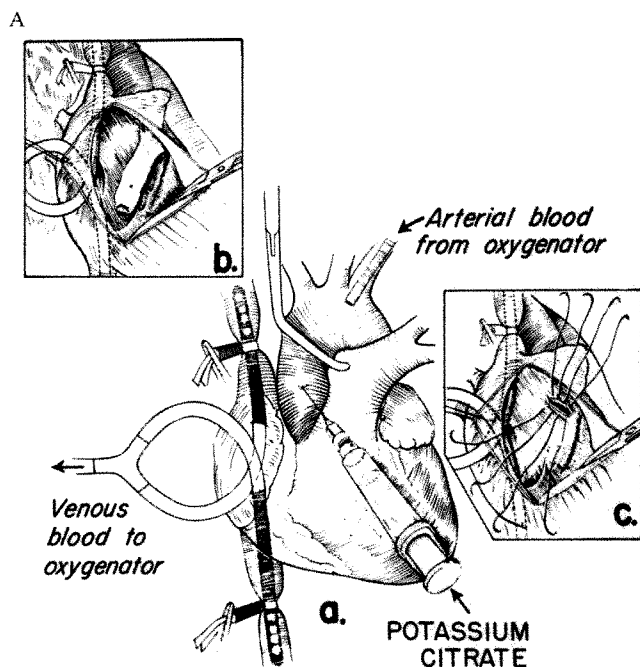
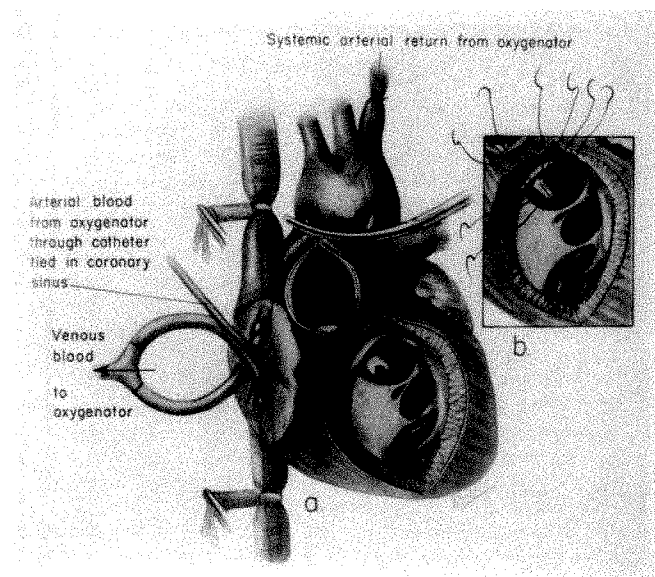


Fig 6. (A) In 1 patient the sinus of Valsalva aneurysm was repaired using an aortotomy and right ventriculotomy that were performed while the heart was supported with retrograde coronary sinus perfusion. (B) In 2 patients hyperkalemic cardioplegic arrest was used to provide asystole during repair of the ruptured sinus of Valsalva aneurysm. (Reprinted from Lillehei CW, Stanley P, Varco RL. Surgical treatment of ruptured aneurysms of the sinus of Valsalva. *Ann Surg* 1957;146:459-72, by permission.)

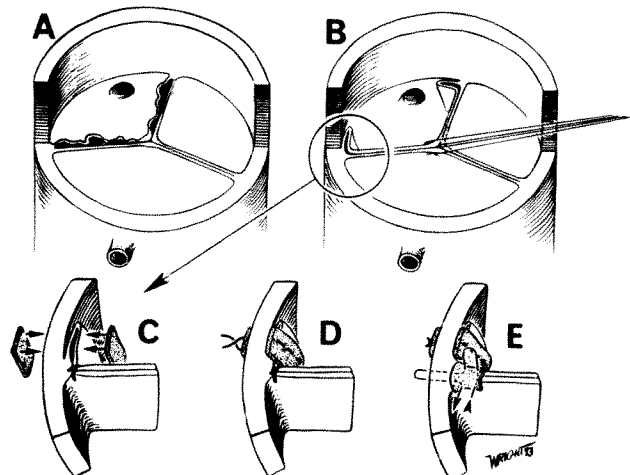


Fig 7. The aortic valve repair as described by Dr Trusler is illustrated. After the aortic valve cusps are aligned, plegeted sutures are used to reduce redundant leaflet tissue. (Reprinted from Trusler GA, Moes CAF, Kidd BSL. Repair of ventricular septal defect with aortic insufficiency. *J Thorac Cardiovasc Surg* 1973;66:394-403, by permission.)

be left untreated at the time of repair, although in the combined experience reported from the University of Alabama at Birmingham and Green Lane Hospital 4 of 17 patients with aortic insufficiency at the time of aneurysm repair eventually required reoperation. Of the patients who required operative treatment of aortic valve insufficiency at the time of aneurysm repair, 4 had Trusler repairs and 1 had repair of an avulsed commissure, whereas 10 patients had valve replacement [20].

Treatment of Unruptured Sinus of Valsalva Aneurysms

Unruptured sinus of Valsalva aneurysms are usually asymptomatic; therefore, the natural history of unruptured sinus of Valsalva aneurysms is impossible to define accurately. In the absence of secure information, the treatment of these aneurysms remains controversial. Extracardiac sinus of Valsalva aneurysms, including aneurysms of the left coronary sinus, are rare and will produce rapidly fatal tamponade upon rupturing. A recent series of 3 such patients was reported from Hospital Broussais in Paris [26]. The excellent results achieved in these patients argue strongly for the repair of unruptured extracardiac sinus of Valsalva aneurysms. The excellent results reported for a small number of unruptured asymptomatic intracardiac sinus of Valsalva aneurysms suggests that surgical treatment may be advisable in light of the potential complications referable to these aneurysms [27, 28]. However, one report of an aneurysm that was monitored without operative intervention for 19 years refutes this notion [29]. Unruptured sinus of Valsalva aneurysms that coexist with cardiac pathology requiring operation are usually corrected at the time of operation [30, 31].

Summary

Congenital sinus of Valsalva aneurysms most commonly rupture into a chamber of the right heart and produce symptoms related to left to right shunting of blood and aortic insufficiency. To solve the surgical problems posed by ruptured sinus of Valsalva aneurysms, Dr Lillehei and associates applied their clinical and experimental experiences with extracorporeal circulation, information regarding the pathology of sinus of Valsalva aneurysms, and data from studies of myocardial protection using retrograde perfusion and cardioplegic arrest. The innovative surgical techniques of extracorporeal circulation and myocardial protection that were used successfully in Dr Lillehei's 3 patients with ruptured sinus of Valsalva aneurysms were subsequently used by scores of cardiac surgeons for treating a variety of other cardiac pathology.

This work was completed during Dr Holman's tenure as an Established Investigator of the American Heart Association.

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Editor's Note

We asked Dr Lillehei for a response to Dr Holman's interesting article

Dr Lillehei's Commentary

It was a pleasure to have this opportunity to read Dr Holman's concise, yet thorough review of all aspects of congenital aneurysms of the sinus of Valsalva. He has summarized very well the anatomy, pathophysiology, associated lesions, surgical techniques for repair, and results of surgical corrections of the ruptured variety.

In the historical note he describes the first successful surgical corrections, all done with cardiopulmonary bypass by our group at the University of Minnesota, using our very simple and very effective disposable bubble oxygenator (see Fig 5). All 3 patients in this initial report were successfully operated on in 1956. One of these early patients has been lost to follow-up, but the other 2, now 37 years since operation, continue to have normal, active lives without cardiac problems related to their birth defect.

It is noteworthy, as Dr Holman has pointed out, that our first patient operated on in May 1956 described the clinical use of retrograde perfusion of the coronary sinus to achieve cardioplegia and to preserve ventricular integrity. We previously had become aware of a report of the Harvard physiologist, H. R. Pratt, published in 1898 (the sixth paper in the first issue of *American Journal of Physiology*) that the myocardium could be nourished from retrograde perfusion of oxygenated blood into the thebesian and coronary veins. As Dr Holman noted, we had thoroughly studied the physiology of retrograde perfu-

sion experimentally [14, 16], confirming Pratt's observations. We then applied this method for the first time clinically in early 1956 in patients with acquired aortic valve disease undergoing open repair, the Valsalva patient noted herein, and to carry out a "modern switch operation" in a baby with complete transposition [14].

Despite our very favorable reports, and those of several others at that time, the method lay clinically dormant for some 25 years! In recent years, retrograde coronary sinus perfusion has achieved widespread recognition among cardiac surgeons and cardiologists as a very valuable method to supply oxygenated blood, cardioplegic solutions, lytic enzymes, or other substances to the ventricular myocardium.

An interesting afterthought for students of the vexing process of creativity is the fact that it sometimes takes a very good idea years to mature and be widely accepted. That observation should be an inspiration to investigators (often young) who may be confused or dismayed by a lack of prompt recognition!

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Inflammatory Response to Cardiopulmonary Bypass

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Cardiac operations with cardiopulmonary bypass cause a systemic inflammatory response, which can lead to organ injury and postoperative morbidity. Causative factors include surgical trauma, contact of blood with the extracorporeal circuit, and lung reperfusion injury on discontinuing bypass. Advances in immunological techniques have allowed measurement of both plasma and intracellular components of this multifaceted perioperative response. This includes activation of the complement, coagulation, fibrinolytic, and kallikrein cascades, activation of neutrophils with degranulation and protease

enzyme release, oxygen radical production, and the synthesis of various cytokines from mononuclear cells (including tumor necrosis factor, interleukin-1, and interleukin-6). Advances in our understanding of the interactions between these markers of cellular and humoral responses to cardiopulmonary bypass will enable more effective intervention to reduce the deleterious effects and improve the outlook for patients undergoing cardiac operations beyond the 1990s.

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In the early 1980s the contribution of complement activation and pulmonary leukosequestration to the morbidity associated with cardiopulmonary bypass (CPB) was the subject of many reports [1, 2]. It was attractive to link the activity of a few measurable markers of humoral and cellular activation to postoperative pulmonary dysfunction. In 1993 we can determine many more markers of the complex and sometimes detrimental consequence of blood contact with artificial surfaces; in addition an "acute phase response" to surgical trauma is increasingly recognized. The purpose of this review is to discuss some of the components of the systemic inflammatory response to CPB and consider how they might relate to the morbidity associated with modern cardiothoracic surgery.

Systemic Inflammatory Response to Extracorporeal Circulation

After exposure of blood to artificial surfaces inflammatory responses are activated including the complement, coagulation, fibrinolytic, and kallikrein cascades. Leukocyte activation occurs and platelet function is impaired. These humoral and cellular systemic responses are manifest in cardiac surgical practice as the "postperfusion" or "post-pump" syndrome with leukocytosis, increased capillary permeability, accumulation of interstitial fluid, and organ dysfunction [1, 2]. Aspects of these responses, their interactions and the implications for lung injury are considered below.

Complement

Complement activation during CPB [1-5] leads to the formation of anaphylatoxins C3a and C5a mainly via the alternative pathway [6]. Activation of the classic pathway (recognized by C4a formation) also occurs at blood/air

interfaces [1] and through the formation of heparin-protamine complexes [7]. Less substantial generation of C3a can be induced by plasmin [8] and kallikrein [9]. The enzyme carboxypeptidase B removes the arginyl residue to form C3a/C5a desArg [6], rapidly reducing C3a activity while C5a desArg continues to have active properties. Operation itself may activate complement [10], but levels of C3a rise dramatically only with commencement of CPB and peak at the end of CPB. Levels of C3a are related to the duration of CPB [2] and return to pre-CPB values after 48 hours. Cardiac and pulmonary dysfunction, renal failure, and bleeding tendencies have been related to C3a levels 3 hours after CPB [2].

Complement activation alone may be insufficient to induce acute lung injury [11], but small amounts of C5a can induce neutrophil aggregation and margination, and the binding of C5a to specific neutrophil membrane receptors [12, 13] (limiting its detection in plasma during CPB) stimulates neutrophil adherence to vascular endothelium [14], potentially important at the time of lung reperfusion. The complement fractions C3b and inactivated C3b, bound to the materials of the extracorporeal circuit, may induce neutrophil degranulation and monocyte release of interleukin-1 β [15]. Additional terminal complement cleavage products (C5b-9) generated during CPB [16] could augment neutrophil activation by stimulation of intracellular arachidonite metabolism [17]. In models of complement activation, leukopenia, increases in pulmonary artery pressure, and impaired oxygenation are accompanied by histologic evidence of sequestration of leukocytes in the capillary bed and endothelial cell damage [18]. Complement-induced capillary injury similarly occurs in models of the adult respiratory distress syndrome [19]. There is no clear consensus on the effects of different types of oxygenator used during CPB on complement activation [20-23].

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Coagulation and Fibrinolysis

Negatively charged surfaces of the CPB circuit and exposed collagen from tissue injury activate factor XII [24]. Factor XIIa can stimulate neutrophil aggregation and exocytosis of elastase [25]. It can generate kallikrein, which induces neutrophil chemotaxis [26], aggregation [27], and degranulation [28]. Kallikrein activates factor XII by positive feedback and induces release of bradykinin, which may cause vasodilation and increased vascular permeability [29]. Fibrinolysis is enhanced during CPB [30], and fibrin-fibrinogen degradation products generated may impair fibrin formation [31] and platelet function [32], and disrupt the endothelial monolayer [33]. In combination these effects might lead to capillary injury, extravascular fluid transudation, and disturbance of normal hemostasis.

Leukocytes

An immediate fall in leukocyte numbers with loss of mature granulocytes and macronuclear cells occurs at the onset of CPB, due to hemodilution or adhesion of neutrophils to the absorbed protein layer in the extracorporeal circuit [34]. Leukopenia is more marked with bubble oxygenation [35]. A later leukocytosis occurs due to mobilization of marginated cells and release of immature neutrophils from bone marrow. This response is abrogated during hypothermia [36].

Neutrophils and lymphocytes remain in the lungs as pulmonary blood flow falls on starting CPB. This early leukosequestration may be a physical property as intrapulmonary neutrophil counts are inversely related to total pulmonary blood flow [37]. As pulmonary blood flow is restored after aortic cross-clamp removal, neutrophils, but not lymphocytes [36], are selectively trapped in the lung capillaries. There is a positive correlation between extent of pulmonary vascular leukosequestration, the length of aortic cross-clamp time, and the total duration of CPB [1]. Bubble oxygenation may initiate significantly more leukocyte sequestration than silicon membrane oxygenation [21]. Sequestration may be a transient phenomenon and is rarely detected with full pulmonary blood flow on discontinuation of bypass [38, 39]. Sequestered neutrophils could be inactive and innocuous [40, 41], but there is evidence that release of lipid peroxidation products (reflecting cell membrane injury) occurs at the same time as pulmonary neutrophil sequestration after removal of the aortic cross-clamp [42].

Primary (azurophil) neutrophil granules containing neutral serine proteases such as elastase, and secondary granules containing several unique glycoproteins including lactoferrin, have important roles in inflammation and host defense that may be relevant in the response to CPB.

Plasma lactoferrin levels peak before CPB [43], and the role of lactoferrin remains uncertain, with potential positive or negative effects on production of oxygen-derived free radicals [44, 45]. A significant role for lactoferrin in the transfer of iron from transferrin into tissue ferritin has been suggested [46], and plasma iron levels are reduced as part of the acute phase response [47].

Neutrophil elastase is of potentially greater importance

due to a high intracellular concentration and low substrate specificity. It is a potent enzyme, and changes in coagulation proteases [48], inactivation of their principal antagonists [49], platelet Gp-Ib hydrolysis [50], and exposure of fibrinogen receptors on the platelet surface [51] are some of its effects that may be relevant to the hemorrhagic complications of prolonged CPB. Elastase has been implicated in neutrophil-mediated endothelial injury in vitro [52] and can initiate the breakdown of the body's own vital tissues if released extracellularly [49].

Elastase release from neutrophils has been reported during CPB [43, 53-55]. An association between pulmonary leukosequestration and increased pulmonary permeability has been reported in dogs after CPB [56], and the capacity for elastase-related lung parenchymal and endothelial injury suggests a potential role for this serine protease in the capillary, pulmonary, and compartmental fluid changes associated with CPB.

Elastase and Antiproteases

To protect against elastase-induced injury, tissues in vivo are bathed in antiproteases. α_1 -Antiprotease, irreversibly inhibiting neutrophil elastase by forming an enzyme-inhibitor complex, plays the major role in elastase regulation because of its high molar concentration in plasma and the rapid inactivation of its major target enzyme [49]. The half-life of elastase- α_1 -antiprotease complex in plasma is about 1 hour [57].

Increased plasma levels of elastase- α_1 -antiprotease complex may be caused by operative trauma [58]. During CPB plasma elastase complex levels rise progressively and peak at the end of the operation [55]. The rise on lung reperfusion may represent washout of activated neutrophils from the pulmonary circulation. Levels are unrelated to peripheral neutrophil counts but do relate to the duration of bypass [54, 59], suggesting neutrophil degranulation or injury during the period of extracorporeal circulation. Despite peripheral neutrophil activation it is probable that intrapulmonary tissue injury is more closely related to intraalveolar elastase release [60, 61].

Oxygen Free Radicals

The defenses against extracellular elastase release may be impaired by oxygen-derived free radicals released during CPB. Free radicals may be neutrophil-derived [62] or produced by xanthine oxidase catalysis of the oxidation of hypoxanthine in reperfused tissues [63]. Subsequent oxidation of the methionine reactive site of α_1 -antiprotease markedly slows the rate of inhibition of elastase and reduces the stability of elastase-inhibitor complexes.

Neutrophils can generate oxygen radicals during CPB by membrane- and granule-related mechanisms. Membrane-bound NADPH oxidase enzyme complex can generate the oxygen metabolites superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radical ($OH^\cdot$) [64]. Primary granule-derived myeloperoxidase catalyzes the oxidation of chloride ion in the presence of hydrogen peroxide to yield hypochlorous acid (HOCl) [65], which has been implicated as a cytolytic mediator. Evidence supporting free radical generation during cardiac opera-

tions is provided by increased plasma lipid peroxidation products after aortic cross-clamp removal [42] and elevated hydrogen peroxide levels at the end of CPB [66]. Peroxidation products may cause direct injury to lipids and nucleic acids, and by denaturing cell surface proteins further augment tissue injury [67].

Endotoxin and Cytokines

Recent interest in acute lung injury has focused on the role of endotoxin and the systemic inflammatory cytokines. Cytokines are endogenous polypeptides produced by a variety of cell types. They serve for signal communication between cells involved in immunity and inflammation and are thought to play an essential role in the pathogenesis of shock and multiple organ failure during sepsis. Monocytes "primed" by sepsis or surgical procedures such as CPB may release systemic inflammatory cytokines including tumor necrosis factor- α (TNF), interleukin-1 β (IL-1), and interleukin-6 (IL-6).

Endotoxins are lipopolysaccharides derived from the walls of degraded gram-negative bacteria. Their biologic effects include activation of the coagulation cascade, complement by both the classic and alternative pathways, the oxidative burst response in neutrophils, and increased adhesiveness of vascular endothelial cells [68, 69]. In vitro, endotoxin induces endothelial cell injury by an elastase-dependent mechanism [52]. In animal models low-dose endotoxin causes transient pulmonary neutrophil accumulation with lung injury if systemic neutrophil activation also occurs [70].

During CPB splanchnic vasoconstriction could lead to intestinal mucosal injury, allowing leakage of endotoxin into the bloodstream while clearance may be impaired after CPB due to suppression of the reticuloendothelial system [71]. In one study, plasma endotoxin was maximal at 90 minutes of perfusion, decreasing significantly 6 hours after CPB and gradually falling until the seventh postoperative day [72]. Another study found gradually rising endotoxin levels during CPB, peaking at the time of aortic cross-clamp removal and falling to baseline levels 45 to 75 minutes after CPB [73]. Endotoxemia during CPB has been related to enhanced generation of free radicals by neutrophils, but there is no obvious relation to postoperative morbidity [74, 75].

In the absence of a rise in plasma TNF a significant endotoxin contribution to postoperative morbidity would be unlikely. Using the limulus amoebocyte lysate assay for endotoxin [76], positive assays have been obtained in "sterile" infusion solutions and concentrated commercial heparin preparations [75] perhaps due to cross-reacting pyrogens for which there are many sources in cardiac operations, including components of the extracorporeal circuit, infusion solutions, and surgical instruments.

Tumor necrosis factor- α is produced by activated monocytes, lymphocytes and Kupffer cells. Known previously as cachectin, it is distinguished from TNF- β (lymphotoxin), a structurally related polypeptide. Factors triggering TNF synthesis include C5a [77], interleukin-1 β [78], gram-negative endotoxin [78], and gram-positive bacterial products [79]. Induction of an acute phase response by

TNF has been demonstrated in vitro, with increased synthesis of hepatic proteins and glycoproteins [80]. It has been implicated in septic lung injury both in animals [81] and in humans [82]. Effects on neutrophils include production of an oxidative burst, degranulation, increased phagocytic activity, and increased expression of leukocyte adhesion molecules [83, 84].

To date reports on the plasma TNF response to CPB have been conflicting. A significant increase in TNF, preventable by dexamethasone administration, has been observed after removal of the aortic cross-clamp [85]. No plasma TNF was detected in another study [86], and although others found detectable plasma TNF in 10 of 19 patients preoperatively there was no significant change during or after CPB [55].

Interleukin-1 β is an important component of inflammatory and immune responses. Factors inducing IL-1 production include complement anaphylatoxins [87] and endotoxin [88]. Adherence to foreign surfaces activates monocyte production of IL-1 [89]. Fever, neutrophilia, and enhanced release of C-reactive protein are mediated by IL-1 [90]. Cultured endothelial cells stimulated with TNF or IL-1 become hyperadhesive for neutrophils [91]. Interleukin-1 β induces release of specific granule contents from human neutrophils [92] and induces synthesis of IL-6 by monocytes [93].

Increased production of IL-1 has been transiently found after CPB, maximal at 24 hours, coinciding with a peak in body temperature [86]. In this study IL-1 production was assessed by measuring functional activity and IL-1 antigen concentration in cell lysates from monocytes of patients during and after CPB. By contrast plasma IL-1 was not detected in two other reports [39, 59], perhaps reflecting a more important role as a paracrine mediator [94]. In general, IL-1 is not detectable systemically during most forms of acute inflammation [95-98].

Interleukin-6 is involved in the modulation of the acute phase response [99]. It is produced by a variety of activated cell types including monocytes [100], lymphocytes [101], and endothelial cells [102]. It induces acute phase proteins in vivo [99] and stimulates the full spectrum of acute phase proteins in adult human hepatocytes in vitro [103]. Interleukin-6 can induce fever [104] and elicit the release of adrenocorticotrophic hormone [105]. It has been detected in serum after burn injury [104], after elective operation [106], and in septic patients [95, 107]. After general operation the serum IL-6 level rises within 2 to 4 hours of surgical incision, and the response correlates with the duration of the operation. Peak levels occur 4 to 6 hours postoperatively [108]. Interleukin-6 may be a sensitive early marker of tissue damage, and levels may be of prognostic value in septic shock [105]. The postoperative rise in IL-6 level may be a protective mechanism as IL-6 inhibits endotoxin-induced TNF production by monocytes [109].

In response to CPB similar rises in plasma IL-6 levels occurred with both membrane and bubble oxygenation [39]. Plasma C-reactive protein (a hepatic acute phase protein) reaches a later peak [55]. After bypass fever, leukocytosis, a negative nitrogen balance, increased vas-

cular permeability, and an increase in the synthesis of hepatic acute phase proteins are all compatible with IL-6 release, and the pattern of the IL-6 response (a 4-hour postoperative peak and sustained elevation at 48 hours [39]) is consistent with a role as a major mediator of the acute phase response to CPB.

Unresolved issues in the measurement of circulating cytokines include effects of binding to plasma proteins, assay inhibition by specific plasma proteins, rapid degradation by plasma proteases, rapid clearance from the circulation by cell receptors, and transiently elevated levels that are easily missed [88]. Interpretation of circulating IL-1 levels is further complicated by the presence of specific plasma inhibitors that act as IL-1 receptor antagonists on target cells [110-112]. Production of IL-1 inhibitor increases as monocytes mature into macrophages [113]. Soluble specific protein inhibitors, possibly shed receptors, have been described for IL-1 [114] and TNF [115]. No IL-6 inhibitor is currently known, but IL-6 does bind to the carrier protein α_2 -macroglobulin.

Intraalveolar Events

Systemic markers of inflammatory responses may not adequately reflect intrapulmonary events after CPB. Determination of intraalveolar free elastase or elastase complex might be better indicators of elastase-related lung injury, but in one study no elastase activity was detected 4 hours after CPB [116]. Timing of the lavage is obviously critical. Intraalveolar TNF and IL-1 have been demonstrated in patients with the adult respiratory distress syndrome [117, 118], but intraalveolar levels of these cytokines have yet to be investigated after CPB.

Therapeutic Intervention

If systemic inflammatory mediators contribute to the morbidity of extracorporeal perfusion, limitation of the intensity of the response should be possible with treatment including corticosteroids, oxygen radical scavengers, neutrophil granule stabilizers, and specific monoclonal antibodies.

Pretreatment with corticosteroids has been claimed to minimize lysosomal enzyme release during CPB, and complement-induced neutrophil aggregation [119] is inhibited *ex vivo* [120]. Both corticosteroids [121] and aprotinin [122] reduce plasma levels of neutrophil elastase after aortic cross-clamp removal, and dexamethasone administration prevents TNF production during CPB [85]. Corticosteroids are not used routinely as prophylaxis during CPB; there is no evidence of effective *in vivo* complement activation inhibition, cellular host defense mechanisms are impaired, and higher endotoxin levels have been reported in treated patients [123].

Reduction of lung injury may be achieved by inhibiting neutrophil activation. Neutrophil depletion by filtration protects against CPB-induced lung injury in animal models [120]. Calcium channel blockers may inhibit neutrophil metabolic pathways involved in the production of injurious substances. The continuous infusion of nifedipine during CPB causes significantly lower levels of elastase-

α_1 -antiprotease complex and lactoferrin but not C3a [53]. In animal studies, the combination of superoxide dismutase and catalase protects host tissues from oxidative damage by activated neutrophils [124]. The antioxidants mannitol and allopurinol reduce hydrogen peroxidase production during clinical CPB [125]. Nonenzymatic free radical scavengers that could be of benefit include vitamins C and E [126]. The iron-chelating agent deferoxamine, binding free iron and thereby interfering with free radical generation, decreases acute lung injury after complement activation [127] and inhibits lipid peroxidation during CPB [128].

Aprotinin (as a nonspecific enzyme-inhibitor) was originally administered during CPB in hope of abrogating the inflammatory response to CPB. A marked reduction in postoperative bleeding was noted [122, 129-131]. Improved hemostasis may have been achieved by inhibition of the plasmin degradation of the platelet membrane glycoprotein Gp-Ib [132]. Although routine use of aprotinin during cardiac operations has been recommended [131], its effect on coronary graft patency has yet to be determined.

If cytokine responses to CPB are important there are several potential therapeutic possibilities. Neutrophils that have been activated with inflammatory cytokines and incubated with the methylxanthine pentoxifylline show decreased superoxide production, decreased degranulation, decreased adherence, and increased chemotaxis [133]. Pentoxifylline inhibits the inflammatory action of IL-1 and TNF on neutrophil function [133]. Models simulating adult respiratory distress syndrome demonstrate a diminution of lung injury if pretreated with pentoxifylline [134-136]. Infusion in human volunteers abolishes the endotoxin-induced rise in TNF (but not IL-6) [137], and pulmonary and cardiac damage are diminished in a model of CPB [138]. However, in a clinical study of CPB, a postinduction infusion of pentoxifylline ($1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) did not significantly reduce plasma levels of elastase complex, IL-1, or IL-6 or improve postoperative oxygenation [59].

Monoclonal antibodies against TNF and IL-1 receptors prevent endotoxin-induced shock in animal models of sepsis [81, 139]. Monoclonal antibodies to endotoxin reduce mortality in gram-negative bacteremia and septic shock in humans [140] and given prophylactically reduce septic shock and mortality in surgical patients at high risk of gram-negative infection [141]. Therapeutic intervention to reduce cytokine-related responses may, however, result in inhibition of T-cell proliferation, B-cell proliferation, and lymphokine generation, thus diminishing host defense and making the patient more vulnerable to severe infection, and there seems no justification for use of monoclonal antibodies to endotoxin in CPB at present.

Conclusion

The whole body inflammatory response to CPB is considerably more complex than it seemed a decade ago. The acute phase response to trauma, in which cytokines are intimately involved, may be an integral part of this

process. Ten years hence, our expanding knowledge of inflammatory mediators may allow a better understanding of CPB-related morbidity, significant improvements in the biocompatibility of perfusion circuits with diminished injurious systemic responses, less lung injury, and an improved outlook for CPB beyond the 1990s.

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1992 Meeting

Southern Thoracic Surgical Association

The Thirty-ninth Annual Meeting of the Southern Thoracic Surgical Association was held at the Saddlebrook Golf and Tennis Resort, Wesley Chapel, Florida, November 5-7, 1992. The President was William A. Cook, MD.

Officers elected for the coming year are: *President*, Gordon F. Murray, MD; *President-Elect*, Ronald C. Elkins, MD; and *Vice President*, Kit Arom, MD.

The following applicants were elected to membership:

Erle H. Austin III, MD
Louisville, KY

George William Johnson, Jr, MD
Houston, TX

Pamela S. Peigh, MD
St. Louis, MO

John C. Austin, MD
Nashville, TN

Roy L. Kingry, Jr, MD
Tyler, TX

Samuel B. Pollock, Jr, MD
Louisville, KY

Frank P. Catinella, MD
Fort Lauderdale, FL

John Thomas Kirchmer, Jr, MD
Beaumont, TX

John D. Randolph, MD
Oklahoma City, OK

Daniel Michael Cohen, MD
Greenville, NC

A. Michael Koury, MD
Jackson, MS

Michael Rosenbloom, MD
St. Louis, MO

Joel D. Cooper, MD
St. Louis, MO

Stephen L. LaMendola, MD
Beaumont, TX

William H. Ryan, MD
Dallas, TX

Edward Frank Crocker, Jr, MD
Lake Charles, LA

Michael Mack, MD
Dallas, TX

Cary L. Stowe, MD
Orlando, FL

Thomas M. Egan, MD
Chapel Hill, NC

Michael R. Mill, MD
Chapel Hill, NC

Stephen L. Wallenhaupt, MD
Winston-Salem, NC

Peter Einstein, MD, PhD
Memphis, TN

Michael Christopher Murphy, MD
St. Louis, MO

Thomas H. Wareing, MD
St. Louis, MO

Elevated to senior membership were: Orville W. Clayton, MD, Roy H. Crispin, MD, J. Ralph Dunn, Jr, MD, William H. Edwards, MD, R. C. Garby, MD, Loyde H. Hudson, MD, Edward W. Jenkins, MD, Charles R. Kessler, MD, Nelson H. Kraeft, MD, Donald E. McDowell, MD, Judson Randolph, MD, Orval E. Riggs, MD, Hasmukh H. Shah, MD, E. Wilson Staub, MD, and Robert J. Wilder, MD.

The President's Award for the best scientific paper given at the 1991 meeting was presented to Ross M. Ungerleider, MD, William Greeley, MD, Ronald Kanter, MD, and Joseph Kisslo, MD, for their paper "The 'Learning Curve' for Surgeons for Evaluating Repair of Congenital Heart Defects Using Intraoperative Echo."

The 1993 meeting will be held at Marriott's Bay Point Resort, Panama City Beach, Florida, November 4-6, 1993. Chairman of the Program Committee will be Harvey I. Pass, MD, Chairman of the Postgraduate Committee will be Constantine Mavroudis, MD, and Chairman of the Membership Committee will be Marion R. Lawler, Jr, MD.

Hendrick B. Barner, MD
Secretary-Treasurer
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Carotid Endarterectomy During Aortic Clamping*To the Editor:*

Weiss and co-workers [1] recently described a technique for combining carotid endarterectomy with a cardiac operation in which cardiopulmonary bypass was used to achieve systemic hypothermia (20°C) for cerebral protection. Both the carotid endarterectomy and the cardiac procedure were carried out during a single period of aortic cross-clamping, and a continuous retrograde infusion of blood was used for myocardial protection. In their report, Weiss and co-workers stressed the advantages of hypothermic cerebral protection during the period of carotid clamping, including elimination of the need for a carotid shunt.

Weiss and co-workers are to be commended for their excellent results (no strokes, 1 death, in 23 patients) with this innovative approach, but certain aspects of their technique merit review and comment. They exposed the carotid artery first and then proceeded with cardiopulmonary bypass, aortic clamping, and continuous retrograde cardioplegia (first warm, then cold). While the patient was being cooled, the early stages of the cardiac procedure were carried out. When a bladder temperature of 20°C was reached, the cardiac procedure was interrupted and the carotid endarterectomy was performed.

They point out that their technique is novel because in previous reports of carotid endarterectomy on bypass, the endarterectomy was performed before aortic cross-clamping while the heart was beating or ejecting. In those other reports, systemic temperatures were lowered only to 28°C to 30°C "lest the heart fibrillate." Weiss and co-workers note that by lowering the systemic temperature further to 20°C they provided an additional decrease in cerebral oxygen requirements and thus enhanced cerebral protection.

We strongly endorse their concept of combined operations with hypothermic cardiopulmonary bypass, and have also used systemic hypothermia in the range of 20°C in 15 patients over the past 2 years. Our approach has been different, however, and we believe far simpler, because we do not clamp the aorta before the carotid endarterectomy as we are unconcerned about hypothermic ventricular fibrillation. The safety of ventricular fibrillation (even at moderate hypothermia of 30°C, not to mention at profound hypothermia of 20°C) has been amply demonstrated in numerous reports of clinical and experimental studies that we have discussed elsewhere [2].

In patients undergoing combined carotid endarterectomy and a cardiac operation, we institute routine cardiopulmonary bypass and vent the left ventricle in the manner we recently reported [3]. While the patient is being cooled to a core temperature of 20° to 22°C, the neck incision is made and the carotid artery is exposed. During this cooling interval, arterial and venous conduits are also harvested and prepared. The endarterectomy is then carried out, although the neck incision is not fully closed until later, after protamine is given. The patient is then rewarmed to 30°C while the cardiac procedure is being performed. If the cardiac procedure is an isolated coronary bypass we generally avoid cardioplegic arrest, although others might prefer to use it in these circumstances, but we do use cardioplegia for valve procedures, usually with a myocardial protection jacket, which—in these combined procedures with prolonged rewarming—is particularly protective against rewarming of the ischemic heart. Aortic cross-clamping is thus limited to the interval necessary for the cardiac procedure, and any unexpected developments that prolong the noncardiac portions of the combined procedure do not prolong aortic cross-clamping.

Although Weiss and co-workers may believe that their tech-

nique of continuous retrograde cardioplegia at 100 mL/min during aortic cross-clamping is sufficient protection, they have reported that 16 of 100 consecutive patients who underwent unspecified cardiac procedures with this technique required inotropic support for more than 24 hours [4]. That requirement suggests that it would be wise to avoid unnecessary aortic cross-clamping, because ischemic myocardial injury does occur even with low-flow continuous cardioplegia, in contrast to the experience with hypothermic ventricular fibrillation at high flow and perfusion pressures [2, 5]. We therefore suggest that consideration be given to our simpler sequential approach to combined procedures, in which carotid endarterectomy is performed on bypass before the aorta is cross-clamped. Whether cardioplegia is later used for the cardiac procedure is a separate matter of the surgeon's preference, but an unfounded reluctance to let the heart fibrillate (even at 20°C) need not dictate the conduct of the entire combined operation.

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References

1. Weiss SJ, Sutter FP, Shannon TO, Goldman SM. Combined cardiac operation and carotid endarterectomy during aortic cross-clamping. *Ann Thorac Surg* 1992;53:813-6.
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*Reply**To the Editor:*

My colleagues and I are delighted that Dr Bonchek's group has been applying this technique in their practice. Although our management of the myocardium differs, the central principle of combining the carotid and cardiac procedures to allow the use of systemic hypothermia to protect the brain during carotid endarterectomy is the same. It is our hope that as more data and technical refinements begin to surface from other institutions, we will all be able to decide if this principle should be adopted into our standard of practice of cardiac surgery.

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Prosthetic Mitral Valve Replacement*To the Editor:*

A recent valve comparison article [1] described a theoretically ideal study design, has valid findings of "not significant" for all

Table 1. Thromboembolism Rates

Variable	SJ	MH
No. of thromboemboli	2	5
Follow-up (patient-years) ^a	121	105
Linearized rate (%/year)	1.65	4.76
95% confidence interval	0.3-5.1	1.7-10.2

^a The patient-years for the two valves in the above table are reversed from those given in the text, which seem to be backwards.

MH = Medtronic-Hall; SJ = St. Jude Medical.

complications, but then concludes that "there is no difference . . . with regard to early clinical results" and that "neither valve can claim superior performance or safety."

All that can be claimed is that the study failed to statistically discover a difference, not that none exists. For a large study, this is sufficient, because a difference of major importance is likely to be discovered. But in a small study, large actual differences may escape statistical detection [2].

This problem can be appreciated by considering confidence intervals for the thromboembolism rates (Table 1). Such a small study can estimate the complication rates for each valve with only very low precision; the confidence interval for each valve spans the spectrum from excellent to poor. Correspondingly, there is a very small chance of finding even a large, real clinical difference to be statistically significant. The confidence intervals overlap tremendously, and the point estimates, although quite different clinically (one is triple the other), are not statistically significant ($p = 0.181$). The fact that clinically significant differences are not statistically so is an alert that the study size may be insufficient.

A study twice as large, with the same rates, would still not quite find significance ($p = 0.059$) but one three times as large would ($p = 0.021$). If this were the case, and it could conceivably happen in this or another study, then one valve could indeed "claim superior performance."

This study is praiseworthy for its design and execution: two current widely used valves and a randomized protocol that allows valid hypothesis tests to be made. But it needs a longer follow-up, more centers, or both. It (so far) can contribute to the above conclusion, but alone cannot support it.

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Reply

To the Editor:

My colleagues and I are grateful to Dr Grunkemeier for pointing out that at the present time our study failed to discover statistical significance between the performance of the Medtronic-Hall and St. Jude prostheses. We agree that a difference may exist between

these two valves, but only with longer follow-up and a larger population size can any definite conclusions be reached.

We are continuing our randomized trial, which was begun in 1986, and at the present time have introduced a second medical center in order that the population size can be expanded. In time, we hope to establish definite conclusions about the performance of these widely used prostheses.

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Thoracoscopic Thymoma Resection

To the Editor:

We read with interest Landreneau and associates' [1] report of thoracoscopic resection of an anterior mediastinal tumor. Their contribution to the developing field of thoracoscopic surgery has already been significant. This is another example of how innovation is requiring us to rethink our approaches to the management of thoracic diseases. It is important for us to continually reexamine both our objectives and our outcomes in the management of our patients, lest we fall into the trap of reduplicating our past successes and failures. Doctor Landreneau and his colleagues in Pittsburgh are to be commended for their efforts in presenting this case report for our consideration.

Because Dr Landreneau's recommendation is both new and controversial, Dr Pairolero's invited commentary is also worthy of consideration. We would agree with Dr Pairolero that long-term survival must not be compromised in the name of less morbid surgery. We take exception, however, to his implication that video thoracic surgical resection is, by nature, limited and diagnostic rather than therapeutic. The resurgence of thoracoscopic surgery is still in its infancy and, because of this, most of



Fig 1. Total thymus specimen containing stage 1 thymoma removed thoracoscopically. The needle points to the thymoma.

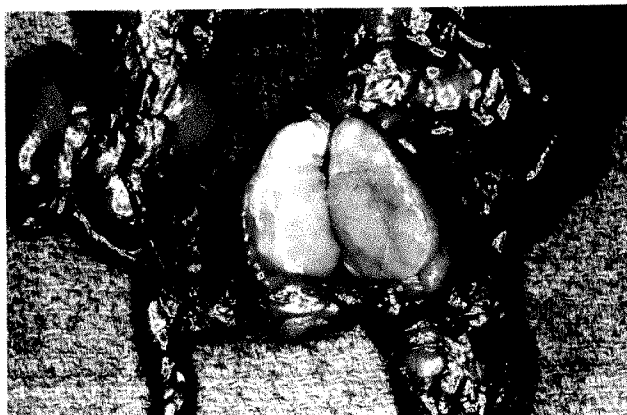


Fig 2. The cut surface of the thymoma shown in Figure 1.

the procedures have been performed for limited indications. We do not think that this is necessarily due to the inherent limited nature of video thoracic surgery, but rather to its stage of development. We see more extensive procedures being performed as more experience is gained.

Regarding thymoma, we think that some of the controversy generated in this article and accompanying commentary could be avoided by total thoracoscopic thymectomy. As shown in Figures 1 and 2, total thymectomy can be accomplished by a thoracoscopic approach. Wider experience is obviously necessary before meaningful comparison with open approaches can be made. We do not believe that any procedure should be compromised or limited *solely* to accomplish it less invasively. If the surgeon believes that the procedure is being compromised by the thoracoscopic approach, conversion to an open, standard procedure should be performed. We believe Dr Landreneau's report continues to advance thoracoscopy into the realm of therapy and anticipate further reports. We would like to congratulate both Dr Landreneau and associates and Dr Pairolero for the stimulating presentation and discussion.

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William H. Ryan, MD
Richard T. Bowman, MD
Mark B. Dou'hit, MD

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Reference

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Reply

To the Editor:

Doctor Acuff and associates, along with Dr Landreneau, are strong advocates of video-assisted thoracic surgery. As Dr Acuff states in his letter, a role for thoracoscopy exists in the management of thoracic disease. The full extent of this role, however, has not yet been determined.

When compared with surgery performed through a thoracotomy, video-assisted surgery is by its very nature limited. Our

eyes and hands are immensely better at determining the gross extent of disease than any videocamera or percutaneous tool. The price, however, is an open procedure with its associated pain, short-term disability, loss of income, and reluctant patient acceptance; thus, the enthusiasm for thoracoscopy.

There is no question that some patients with benign disease, such as those with an indeterminate pulmonary nodule that proves to be a granuloma or hamartoma, are benefited by video-assisted thoracic surgery. But can the same be said for patients with malignant disease, especially those with primary lung cancer? At present this question remains unanswered. Thoracotomy with resection for malignant disease has had a known long-term track record and must be the gold standard against which other therapeutic modalities are measured. In contrast, *no* track record currently exists for thoracoscopic cancer resection other than the enthusiasm of both patient and surgeon.

We all agree that the boundaries of video-assisted thoracic surgery should be expanded; however, they must be pushed back by well-controlled scientific studies rather than by zealous enthusiasm. Thus far, nearly all reports have dealt only with the ability to perform the procedure. Most investigators, including Drs Landreneau and Acuff, do not address the question of how to manage malignancy discovered at thoracoscopy. Instead, they convey the impression that local thoracoscopic excision translates into adequate cancer treatment, a position that is not supported in fact. Until follow-up data become available, this new therapeutic modality should be approached with cautious optimism, for clearly it has *not* withstood the test of time.

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Resection of Mycotic Lung Sequestra After Invasive Aspergillosis

To the Editor:

We would like to add a case report of our own and some comments to the superb experience recently published by Young and associates [1].

A 38-year-old female patient was seen in May 1991 with an acute lymphocytic leukemia. The remission obtained with induction chemotherapy was hematologically but not cytogenetically complete. Hence, a bone marrow transfer was indicated. During the neutropenic state, invasive pulmonary aspergillosis occurred. Initially, several bilateral nodules developed, and two left upper lobe lesions were rapidly cavitating. The patient was treated with intravenous liposomal amphotericin at $3 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ for 56 days (total dose of 7,435 mg); all but the two left upper lobe lesions apparently healed. Operation was considered because of a concern of relapsing aspergillosis from this reservoir during aplasia. The two cavities measured 2 and 3 cm on chest views, and there were no signs of pleural sequelae. The patient was operated on through a muscle-sparing posterolateral thoracotomy. No pleural adhesions were observed. Both lesions were easily identified on palpation and excised with stapled wedge resections using a GIA device to avoid intrapleural seeding. Both cavities contained necrotic tissues mixed up with *Aspergillus* filaments. Postoperative recovery was uneventful, and the patient underwent subsequently successful genoidentical bone-marrow transplantation 6 weeks later; no infectious complications were noted.

Traditionally, operation has been limited to the pulmonary aspergilloma developed in sequelary lesions, either because of troublesome symptoms or prophylactically [2]. Resection of mycotic lung sequestra is a recent issue [3]. As do Young and associates, we affirm that operation has a definite place in the management of cavitary disease after invasive aspergillosis. The rationale of operation is prevention of both hemoptysis and elapsing aspergillosis during subsequent marrow-depressing treatments. This attitude is encouraged by a low operative risk: these mainly young patients have few pleural adhesions (source of bleeding), and elasticity of the lung and mediastinum is normal, prone to correct pulmonary expansion after resection [2].

However, we cannot entirely subscribe to the pathogenesis advanced for hemoptysis associated with invasive aspergillosis. Young and associates hypothesize that bleeding was due to erosion of parietal vessels, as opposed to classic aspergilloma, where the bleeding would originate from the bronchial vessels. We do believe that the principal source of bleeding in invasive aspergillosis is disruption of either bronchial or pulmonary vessels. Erosion of parietal vessels is a most common phenomenon in pulmonary aspergillomas. The chronic cavities are surrounded by a huge vascular network developed as well during the initial disease (mostly tuberculosis) as by the presence of the mycetoma. The large variety of parietal pedicles feeding into this mycetoma-like vascular sponge explains the failure of preoperative embolization to prevent intraoperative bleeding [2, 4].

Again, we would like to compliment their most interesting and important publication.

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Georges Morand, MD*

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Reply

To the Editor:

We thank Massard and colleagues for their comments and note their success in resection of a case of cavitating invasive aspergillosis [1]. Their case confirms the key importance of the development of cavitation in the natural history of invasive pulmonary aspergillosis. Those lesions in which cavitation had not developed resolved with intravenous amphotericin. As in our experience [2], they identified cavitation as the step that indicates reversibility of the process and as the portent of hemoptysis.

The origin of bleeding in classic aspergillomas has not been fully resolved, and we did not wish to suggest that it was

exclusively of bronchial origin. However, most authors would agree that the principal origin of major hemoptysis is the bronchial circulation [3, 4], although there may be extensive collaterals [5]. Bleeding from classic aspergillomas may on occasion arise from vascular inflammatory pedicles extending from the chest wall to the wall of the cavity [6]. We suggest, however, that direct erosion of intercostal arteries is much more likely in cavitating invasive aspergillosis. The pulmonary infarct, which gives rise to the cavity, extends to the chest wall and, in many cases, the chest wall forms one wall of the cavity. The intercostal artery thus commonly lies exposed in the wall of the cavity, an unusual occurrence in classic aspergilloma. However, as with classic aspergilloma, bleeding may have more than one origin, and successful embolization of bronchial arteries in a case of cavitating invasive aspergillosis has been reported [7].

We thank Massard and colleagues for their constructive comments and look forward to the publication of their article on pleuropulmonary aspergillosis.

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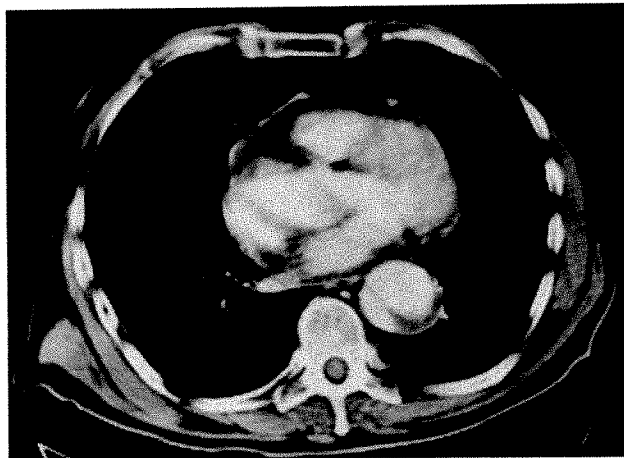
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Thoracic Aortic Dissection and Atherosclerotic Abdominal Aortic Aneurysm

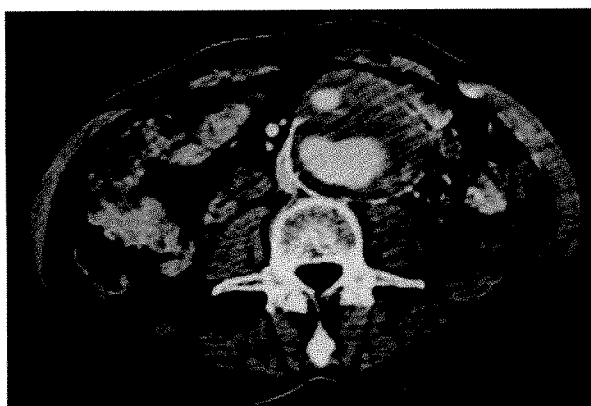
To the Editor:

I read with interest the article by Roberts and Roberts entitled "Combined thoracic aortic dissection and abdominal aortic fusiform aneurysm" [1]. My colleagues and I have operated on an additional case of this uncommon association of abdominal atherosclerotic aortic aneurysm (AAA) and thoracic aortic dissection.

A 63-year-old man was transferred from another hospital for surgical therapy of a ruptured AAA. He had a history of systemic hypertension, gastroduodenal ulcer, right nephrectomy, and chronic renal insufficiency and had been in a program of hemodialysis since May 1988. He also had previously been diagnosed as having a silent infrarenal AAA 5 cm in transverse diameter



A



B

Fig 1. (A) Computed tomographic scan of the descending thoracic aorta with a flap typical of dissection. (B) Computed tomographic scan of the abdomen showing an atherosclerotic abdominal aortic aneurysm with calcification of the arterial wall and with dissection of the anterior aspect of the aneurysm.

(ultrasound examination). The patient experienced acute abdominal pain and hypotension. A thoracoabdominal scan showed dissection of the descending thoracic aorta and infrarenal AAA with a perianeurysmal liquid collection (Fig 1).

On February 2, 1989, the patient underwent operation on an emergency basis, and a median laparotomy was performed. A leaking infrarenal AAA 8 cm in transverse diameter was found. The infrarenal aorta and iliac arteries were clamped, and a straight 22-mm vascular graft was interposed. At the level of the proximal anastomosis the abdominal aorta was clearly dissected with a wide separation between the arterial walls. The true lumen was localized, the graft was sutured in a continuous fashion with suture buttressed with two strips of Teflon felt, and the distal anastomosis was done in the usual manner opposite the ostium of the iliac arteries. The operation was performed without difficulties, and the patient was extubated 48 hours after operation. Because of respiratory and cardiac depression the patient was reintubated, and he died 12 days after the operation due to severe anoxic cerebral-related disturbances. The vascular graft was performing correctly at any time.

Postmortem examination showed a chronic aortic dissection starting in the left subclavian artery in association with a repaired

atherosclerotic infrarenal AAA. The graft was correctly placed. In retrospect, our patient had a remote nondiagnosed type B aortic dissection in association with a ruptured atherosclerotic AAA.

I agree with Roberts and Roberts [1] regarding the infrequent association of combined AAA and thoracic aortic dissection in the same patient and the scarcity of reports about this subject. Our case has some resemblances with the cases reported by Roberts and Roberts [1, 2] and has recently been published [3]. I believe this report can be useful for readers interested in aortic surgery and stress the importance of keeping in mind the eventuality of the association of AAA and thoracic aortic dissection, considering, from theoretical grounds, the possibility of an increasing number of cases in the future, and the necessity and recommendation of full investigation (computed tomographic scanning) of the whole aorta before an aortic operation.

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Treatment of AIDS-Related Bronchopleural Fistula by Pleurectomy

To the Editor:

Crawford and associates [1] have emphasized the advantages of early and aggressive surgical treatment of spontaneous pneumothoraces and persistent bronchopleural fistula associated with acquired immunodeficiency syndrome (AIDS). I share their enthusiasm for early surgical intervention, which includes a parietal pleurectomy and diaphragmatic abrasion in addition to closure of the bronchopleural fistula. This approach has evolved because patients with AIDS are surviving longer and thus are at risk for development of multiple recurrent pneumothoraces [2]. This is illustrated by a representative case demonstrating the progressive course of *Pneumocystis carinii* pneumonia associated with AIDS.

The patient was a 34-year-old man first seen in June 1989 after suffering a spontaneous left pneumothorax following a bout of violent coughing. The patient had a history of AIDS, *Pneumocystis carinii* pneumonia treated with aerosolized pentamidine, disseminated histoplasmosis, and pancytopenia. A chest tube was placed with reexpansion of the lung, but a bronchopleural fistula persisted for 14 days despite attempts at chemical pleurodesis. He was taken to the operating room, and closure of the bronchopleural fistula along with pleurectomy was performed. Chest radiograph after this revealed expansion of the lung with minimal cystic changes of *Pneumocystis carinii* pneumonia (Fig 1). In August 1989 he had a right pneumothorax, which was treated with thoracotomy, closure of the fistula, and pleurectomy. Chest radiograph taken at this time revealed progression of the pneumatoceles bilaterally. The patient was admitted to the hospital in

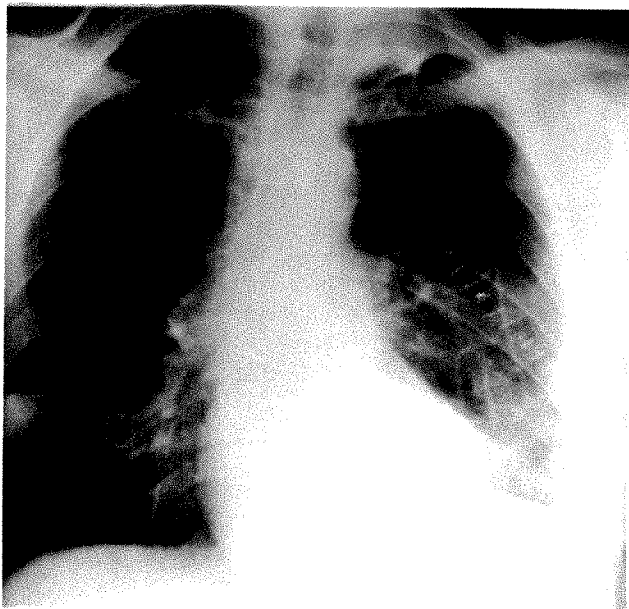


Fig 1. Chest roentgenogram after pleurectomy and closure of bronchopleural fistula.

December 1989 for the last time with marked progression of the pneumatoceles (Fig 2), pancytopenia, and overwhelming sepsis. He died January 8, 1990, approximately 6 months after his initial presentation.

Much has been written concerning the association of *Pneumocystis* pneumonia and AIDS. *Pneumocystis carinii* pneumonia in association with AIDS seems to be more prone to the development of pneumothoraces, probably due to the prolonged course

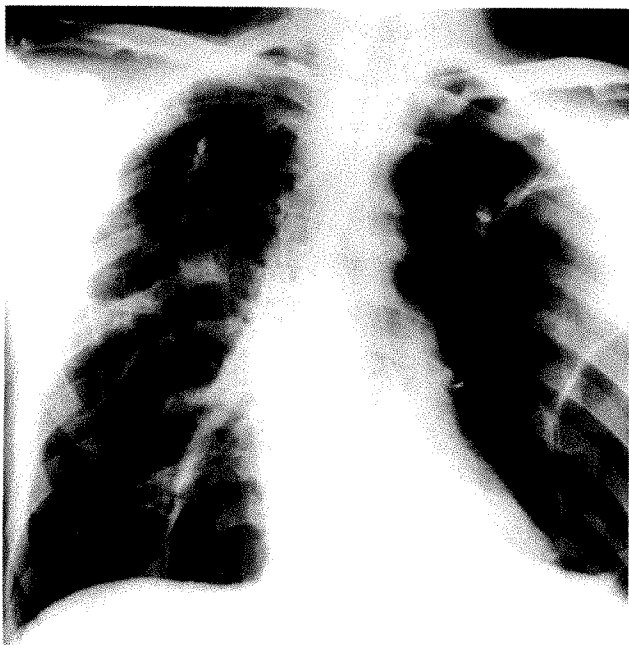


Fig 2. Chest roentgenogram showing marked progression of pneumatoceles.

of infection and the cytotoxic effects of human immunodeficiency virus directly on the pulmonary parenchyma [3]. These pulmonary changes can be progressive and are not avoided by aerosolized pentamidine administration. The pentamidine, in fact, is thought possibly to be associated with a higher incidence of pneumothorax due to the uneven distribution of the drug, with subsequent progression of the disease in the lung apices [4].

The case presented illustrates what can be a virulent replacement of lung parenchyma with pneumatoceles due to *Pneumocystis carinii* pneumonia. These pneumatoceles are prone to rupture with resulting recurrent pneumothoraces, and are not confined anatomically to the apices. Because of the often progressive course of the lung destruction associated with AIDS and *Pneumocystis carinii* pneumonia, I believe that thoracotomy should be considered with the first spontaneous pneumothorax. The operation should include closure of the bronchopleural fistula and attempts to induce pleural symphysis through aggressive parietal pleurectomy. This approach will give the greatest chance of avoiding future pneumothoraces and subsequent operations, should the pneumatoceles due to the *Pneumocystis carinii* increase.

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Staged Expanding Pulmonary Artery Band

To the Editor:

We have read Warren and associates' article [1] in *The Annals of Thoracic Surgery* with great interest. The concept, though, of a simple band closed with several sutures with a controlled distance in between in such a way that the outer suture holds the banding at an increased diameter when the inner one ruptures is not new. We published a study of this concept in a series of articles between 1988 and 1990 [2-4]. We used a regular 4-mm-wide Dacron tape with a radiopaque elastic rubber string in it, and closed it with several single transverse mattress sutures of 5-0 polypropylene. Thus no new engineering was introduced into the banding concept, eg, as in the work of Vince and associates [5, 6]. We evaluated the method in vitro [2] and in a canine experimental study [3], in which the pulmonary artery was banded and long-term follow-up was performed.

Topics in the discussion of Warren and associates' article [1] were the need for human clinical trials, the fact that there is no definite physician's control over the timing of the release of the sutures, suggestions of balloon dilation of the band, and concern about the role scar tissue may play in dilatability. We would like to point out that these very concepts have already been pursued in our institution as mentioned above. Our clinical experience was published 3 years ago [4]; balloon dilation makes the inner

suture rupture. Scar tissue has been no problem in humans. The pulmonary artery does widen. The gradient is being reduced, and the lung flow increased correspondingly.

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Reply

To the Editor:

I was unaware of the *Cardiovascular and Interventional Radiology* literature concerning this subject; however, in our study, we attempted to develop a technique in which no further intervention would be necessary such as balloon dilation or adjusting the volume of a reservoir. Doctor Bjørnstad and associates' technique of balloon dilation would certainly be an advantage if our technique failed to expand the band with systemic pulmonary artery pressure. We were also gratified to see that Dr Bjørnstad and associates had no problems with scar tissue in human trials, and hopefully our technique will not require balloon dilation if the band expands properly.

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Transthoracic Balloon Pumps

To the Editor:

I read with interest the article by Hazelrigg and associates [1] reporting their transthoracic intraaortic balloon pump (IABP) insertion techniques and impressive results. It is noteworthy, however, that they inserted the IABP by the transthoracic route

almost twice as often as they did by the femoral route in their overall series during this interval.

My colleagues and I have reserved transthoracic IABP insertion for only those patients who have major lower extremity ischemic disease or in whom we have been unable to place the IABP by the femoral route. However, when necessary, we have used a technique similar to that described by Hazelrigg and associates. Like them, we insert the balloon through a stab wound between pledged sutures and advance it into the proximal descending aorta. Previously, we obtained an intraoperative roentgenogram, but the radiopaque tip in most IABPs shows only the distal extent of the balloon, which we have generally attempted to place near the diaphragm, with monitoring of the left radial pulse. More recently, we have used transthoracic echocardiography for localization of the balloon.

There is one minor technical modification that we have found useful for IABP removal. At the time of insertion, rather than tying the pledged pursestrings, we have snared those sutures around the shaft of the IABP, using the snares themselves to help secure the catheter and to prevent subsequent migration with pulsation. This is basically the same technique we use for standard aortic cannulation for cardiopulmonary bypass. The suture protruding from the end of the snare is turned down along the shaft of the snare and secured with a large Weck clip. This has allowed us to leave those snares in the chest while the IABP is in place. As described by Hazelrigg and associates, the shaft of the IABP catheter exits from the lowermost portion of the sternotomy incision.

When the time comes for IABP removal, the clips on the snare can be released, and the already placed pursestring can be tied after the balloon has been removed, similar to the way in which we decannulate the aorta at the end of standard cardiopulmonary bypass. This eliminates associated blood loss or the need for application of a partial occlusion clamp, a particular advantage in the patient who frequently has a number of proximal coronary bypass grafts or a diffusely diseased aorta.

Dr Hazelrigg and his co-authors are to be congratulated on their excellent series.

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Reference

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John Gibbon and His Heart-Lung Machine*

To the Editor:

This letter is directed to the attention of your subscribers who have purchased or read my book *John Gibbon and His Heart-Lung Machine* (Philadelphia: University of Pennsylvania Press, 1991). Doctor Bernard J. Miller, who worked with Dr Gibbon, has recommended the following changes. These changes will be incorporated into any future editions of the book, by arrangement with the University of Pennsylvania Press.

1. Doctor Miller pointed out that I had not cited the source for the quotation on page 112, "Animal experiments using the

* Reprinted from *Tex Heart Inst J* 1992;19(3):245, by permission.

Model II were only moderately successful," and for the description of the laboratory respirator. The source for this information is: Miller BJ. The development of heart lung machines. *Surg Gynecol Obstet* 1982;154:403-14. I regret this unintentional omission.

2. The respirator using negative pressure to assist expiration, as described on page 112, should be attributed to Dr Miller.[†] Doctor Miller made modifications to the animal-laboratory respirator that enhanced gas exchange and contributed to lower mortality rates following its adoption. A full description of Dr Miller's respirator can be found in: Miller BJ. A respirator for laboratory animals utilizing compressed air and suction. *Surgery* 1957;42:722-5.
3. Doctor Miller recommends that the section on pages 166-7 (involving "Dr. X") be deleted.

In these instances, Dr Miller's wishes will be carried out.

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Pericardioperitoneal Shunt for Persistent Effusions

To the Editor:

We read with interest the article by Molnar and Jeyasingham [1]. In the last 2 years we performed a similar procedure on 7 patients with persistent pericardial effusion, and achieved excellent palliation. The only modification in our technique is that after excising the pericardial patch, we run a continuous Vicryl (Ethicon Ltd, Edinburgh, UK) suture around the edge of the window joining the pericardial and the peritoneal edges. We pass a drain through the window, which exits through the abdominal wall. This drain is removed when the amount of drainage is minimal. None of these patients had clinical evidence of recurrence of the effusion.

It has been shown [2] that the success of a window is dependent on the inflammatory fusion of the pericardium to epicardium and not maintenance of a window, and that tube decompression should be maintained only until fluid output is minimal to allow apposition and fusion of the two surfaces. Therefore, we do not see the need to maintain a permanent drain in the site;

[†] In connection with item #2, a copy of a letter of confirmation from Dr George J. Haupt will be placed on file at the University of Pennsylvania Press offices before implementation of the recommended change.

indeed, it may not be necessary to form a pericardioperitoneal connection at all.

Mohammad Bashar Izzat, FRCS
Brian Prendergast, FRCS
James A. C. Thorpe, FRCS

Department of Cardiothoracic Surgery
Northern General Hospital
Herries Rd
Sheffield S5 7AU
United Kingdom

References

1. Molnar TF, Jeyasingham K. Pericardioperitoneal shunt for persistent pericardial effusions: a new drainage procedure. *Ann Thorac Surg* 1992;54:569-70.
2. Sugimoto JT, Little AG, Ferguson MK, et al. Pericardial window: mechanisms of efficacy. *Ann Thorac Surg* 1990;50:442-5.

Reply

To the Editor:

The modification in pericardioperitoneal shunt procedure proposed by Izzat, Prendergast, and Thorpe is sensible and advisable in benign cases. One has to keep in mind, however, that differences exist in the adhesion and apposition forming tendencies between the thoracic and abdominal cavities. The drain was used to keep open the peritoneal face of the communication hole. Our main goal was to avoid external drainage and consequent decreased quality of life of patients with limited life expectancy.

The procedure theoretically could be improved by using a circular stapler for creation of a persistent pericardioperitoneal communication. Another possibility is to use a laparoscopic technique in the same manner as the pericardiopleural window is done [1].

Thomas F. Molnar, MD
Kumarasingham Jeyasingham, FRCS

Department of Thoracic Surgery
Frenchay Hospital
Bristol BS 16 1 LE
United Kingdom

Reference

1. Ozuner G, Davidson PG, Isenberg JS, McGinn JT. Creation of a pericardial window using thoracoscopic techniques. *Surg Gynecol Obstet* 1992;175:69-71.

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Cardiothoracic vascular surgeon, board certified or board eligible, to join well-established, busy one-man private practice in Midwest. Salary leading to partnership. Please send CV and references.

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Please reply with curriculum vitae and bibliography to Hermes C. Grillo, MD, Chief of General Thoracic Surgery, Massachusetts General Hospital, Boston, MA 02114. Harvard Medical School and Massachusetts General Hospital are affirmative action/equal opportunity employers. Women and minority candidates are encouraged to apply. 806L/B

The Division of Thoracic and Cardiovascular Surgery at the University of New Mexico School of Medicine in Albuquerque is seeking applications for a full-time faculty position at the Assistant/Associate Professor level for July 1993. We are looking for an individual with excellent skills in adult cardiac surgery and with specialized training in cardiac transplantation. The candidate must be board eligible or certified and have strong interest in research and teaching. This is an excellent opportunity for an individual interested in academic achievements as well as a good clinical experience.

Please forward curriculum vitae and three letters of recommendation to Jorge A. Wernly, MD, Chief, Division of Thoracic and Cardiovascular Surgery, University of New Mexico Medical Cen-

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Noncardiac thoracic and vascular surgeon, BE/BC, to join established one-man private practice on Florida's southeast Gold Coast. Send CV and details of experience.

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Thoracic and vascular surgeon, BC/BE, needed for community practice in Northeast. No cardiac surgery. Please send CV.

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Cardiothoracic and vascular surgeon to join a well-established three-man adult CV practice in California's Central Coast. Applicant must be BE/BC. Recent graduate of university program preferred. Please respond with CV.

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Cardiovascular surgeon wanted to join three surgeons in an established adult cardiac, thoracic, and vascular surgery practice in north central Texas. Must be board certified/eligible. Salary plus benefits with full partnership available. Please send resume and references.

Please respond to Box 828. 828A/C

Faculty/academic position: The Division of Cardiothoracic Surgery, University of Washington, is seeking a BC/BE, adult cardiothoracic surgeon. The individual will have a dual appointment at University Medical Center and the Veterans Administration Medical Center. He/she will be responsible for continuing the VA clinical, educational, and research programs. He/she should have

demonstrated a strong clinical cardiac surgery background and commitment to education and research. AA/EOE.

Send complete curriculum vitae to Edward D. Verrier, MD, Division of Cardiothoracic Surgery, RF-25, University of Washington, Seattle, WA 98195. 834A/B

Academic general thoracic surgeon: The Division of Cardiothoracic Surgery and the Section of Thoracic Surgery invites applications and nominations for a faculty position in general thoracic surgery at the University of Washington. Prospective candidates should be American Board of Thoracic Surgery eligible or qualified as of July 1, 1993, have demonstrated excellence in clinical surgery and research, and possess a commitment to teaching. Preference will be given to those who have broad experience in general thoracic surgery including lung transplantation. The successful candidate will be involved in the clinical programs at the University of Washington Medical Center, Harborview Medical Center, and Seattle Veterans Administration Hospital in Seattle as well as becoming actively involved in the Lung Transplant Program, the Cardiothoracic Surgery Laboratory, and in participating in the Thoracic Surgery clinical trials.

Applicants should have their curriculum vitae sent to the following address: Douglas E. Wood, MD, Chief, Section of Thoracic Surgery, University of Washington, Division of Cardiothoracic Surgery, SA-25, Seattle, WA 98195. University of Washington is an equal opportunity, affirmative action employer. 836A/B

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Please forward curriculum vitae or recommendations to A. Gerson Greenburg, MD, PhD, Chair Person, Search Committee, The Miriam Hospital, 164 Summit Ave, Providence, RI 02906. 842B/D

Emory University Department of Surgery, Division of Cardiothoracic Surgery, Atlanta: currently seeking candidate for faculty at assistant professor level in adult cardiac surgery with a particular interest in diseases of the aorta. Candidates must be board certified in general surgery and board certified or eligible in thoracic surgery and have a strong academic and research focus. Women and minorities are encouraged to apply.

Please submit CV and letters of recommendation to Robert A. Guyton, MD, Chief, Division of Cardiothoracic Surgery, The Emory Clinic, 1365 Clifton Rd, NE, Atlanta, GA 30322. Emory University is an affirmative action, equal opportunity employer. 844B

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Please send CV and direct questions to M. Terry McEnany, MD, Chief, Department of Cardiovascular Surgery, Kaiser-Permanente Medical Center, 2350 Geary Blvd, San Francisco, CA 94115; (415) 202-3800. 826A/D

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Please send a CV and letters of recommendation to George J. Magovern, MD, Professor and Chairman of Surgery, Allegheny General Hospital and the Allegheny Campus of the Medical College of Pennsylvania, 320 E North Ave, Pittsburgh, PA 15212. 827A/D

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Interested applicants should send CV to Ed Verrier, MD, Associate Professor and Chief, Division of Cardiothoracic Surgery, SA-25, University of Washington, 1959 NE Pacific Ave, Seattle, WA 98195. 832A/B

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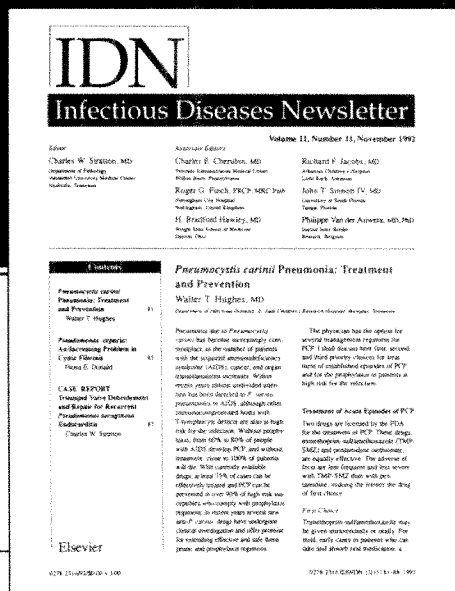
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Please send inquiries with curriculum vitae to Gerald M. Lawrie, MD, One Baylor Plaza, Department of Surgery, Houston, TX 77030. Baylor College of Medicine is an equal opportunity/affirmative action/equal access employer. 843B

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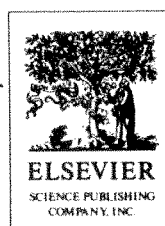
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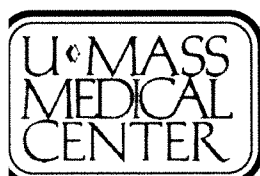
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Please respond with curriculum vitae to: Thomas J. Vander Salm, M.D., University of Massachusetts

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Cardiothoracic Surgeon

The Department of Surgery at the Dartmouth-Hitchcock Medical Center in Lebanon, New Hampshire is searching for an additional academic Cardiothoracic Surgeon at the Assistant/Associate Professor level. Candidates for this position must be BC/BE in Thoracic Surgery and should have demonstrated, by prior training and expertise, superior skills in all aspects of adult and pediatric cardiac surgery as well as general thoracic surgery. The physician will be responsible for the care of patients in an established cardiothoracic practice at The Hitchcock Clinic with privileges extended to the Veterans Administration Hospital in White River Junction, Vermont.

The successful candidate should have demonstrated a commitment to research by previous experience and publications and will have the opportunity for further academic pursuits, including the education and training of medical students and house staff physicians. The individual will be an employee of The Hitchcock Clinic and will receive an appropriate academic appointment as a member of the faculty of Dartmouth Medical School. DHMC is an AA/EO employer and is especially interested in identifying female and minority candidates.

Inquiries and resumes should be directed to Charles A.S. Marrin, M.B., B.S., Chairman, Cardiothoracic Surgery Search Committee, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire 03756, (603) 650-7390.



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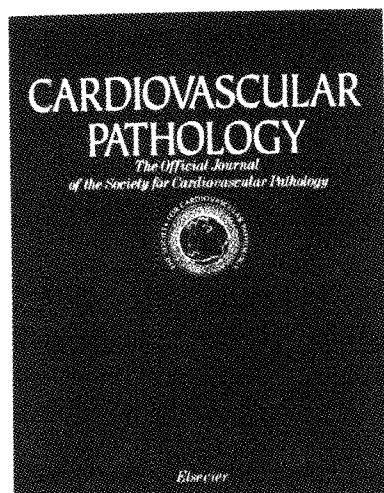
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- Further Morphological Observations on Hearts With Twisted Atrioventricular Connections (Criss-Cross Hearts), *J.W. Seo, S.J. Yoo, S.Y. Ho, H.J. Lee, and R.H. Anderson*

Cardiovascular Pathology is abstracted in CABS/Current Awareness in Biological Sciences.

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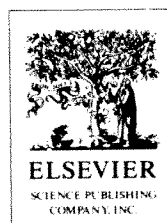
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*Official Journal of The Society of Thoracic Surgeons
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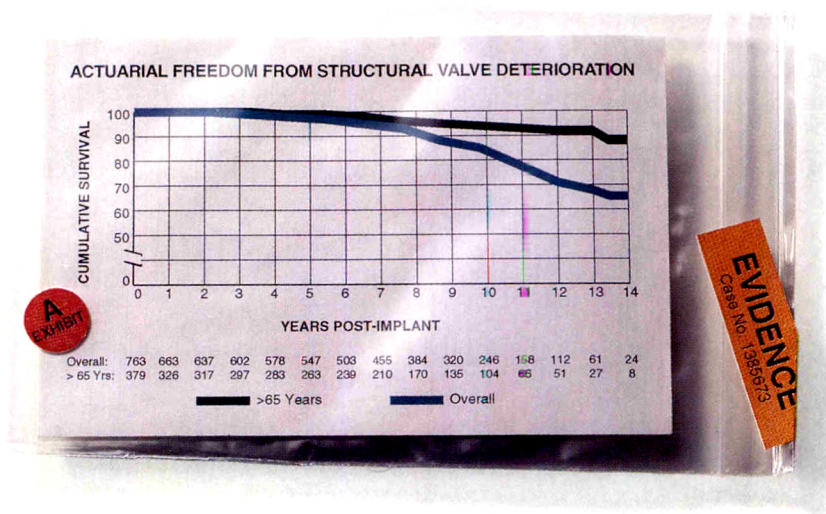
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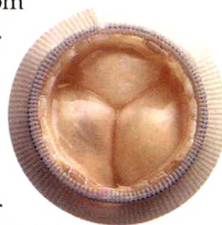


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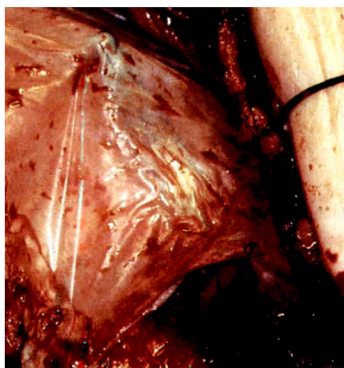
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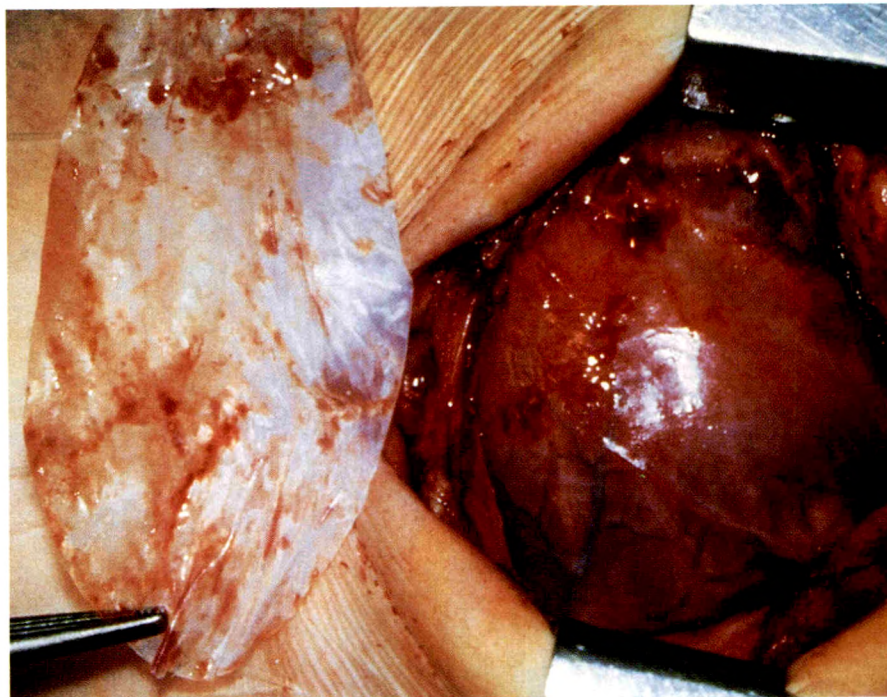
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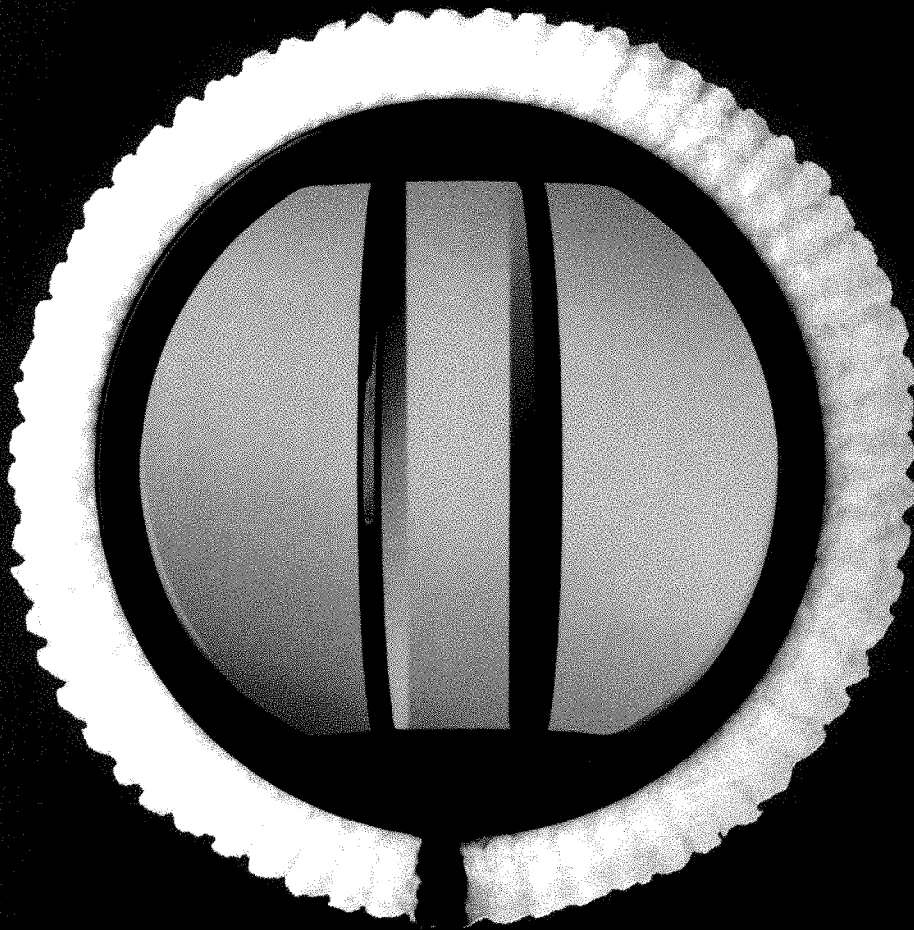
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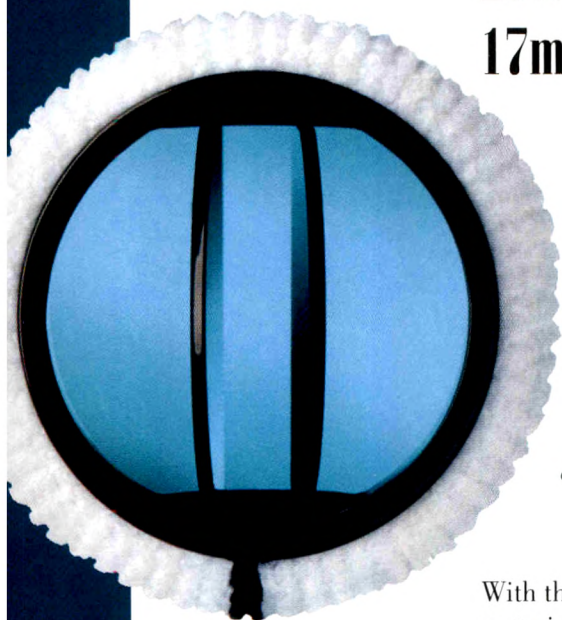
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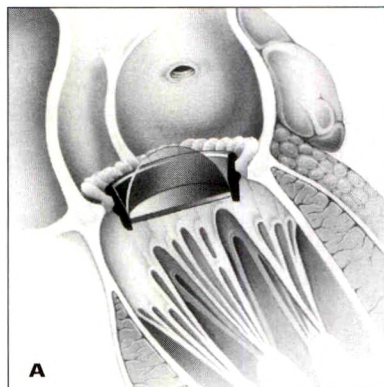
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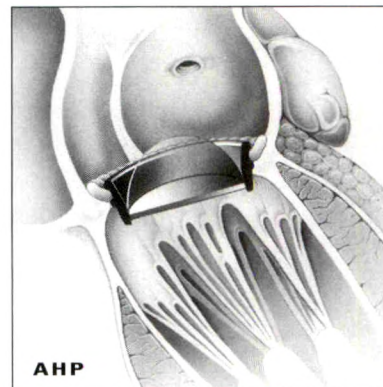
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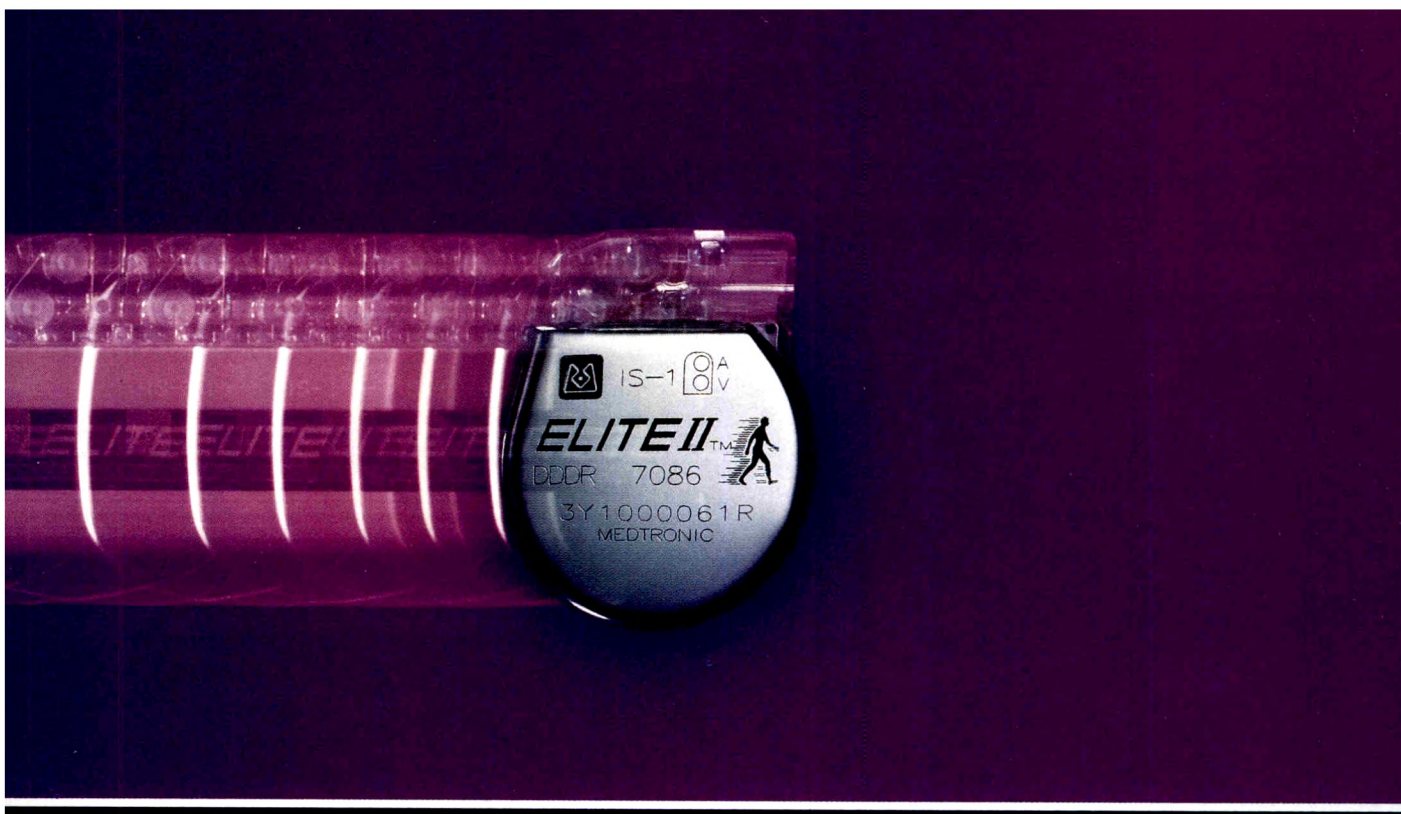
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INTENDED USE: The ELITE II™ dual chamber pacemaker is for therapeutic management of heart rate disorders when restoration of AV synchrony or the need for rate response is indicated. The DDDR, DDIR, and DMR pacing modes are for persistent sinus brady, uncontrollable brady-tachy syndrome, and sinus pause/arrest. The AAIR mode is for sinus node dysfunction and intact AV conduction. The VVIR mode is for chronic atrial flutter or fibrillation with a slow ventricular response, certain atrial or ventricular arrhythmias, or situations where it is desirable to disable the atrial channel (e.g., inexcitable atrium). See product labeling for a detailed list of intended uses for the 19 pacing modes available.

CONTRAINDICATIONS: In the presence of chronic atrial flutter or fibrillation, the DDDR, DDD, DDIR, and DDI modes may be contraindicated and atrial pacing in the DMR and DM modes is ineffective. The AAIR, AA, AAT, AOC, and AOO modes are contraindicated in the presence of AV conduct disturbances. The asynchronous pacing modes are contraindicated if competition between paced and intrinsic rhythms is likely. Do not use steroid eluting leads in patients for whom a single dose of 1.0 mg dexamethasone sodium phosphate may be contraindicated.

WARNINGS: Do not use diathermy over the pacemaker or defibrillation paddles within 12 cm of the pacemaker; damage to the pacemaker's electronic components may result. Do not use electrosurgical units within 15 cm of implanted pacing systems; this may introduce fibrillatory currents into the heart. Confirm pacemaker operation after diathermy, defibrillation, or electrosurgical procedures.

PRECAUTIONS: Electrical discharges from implantable cardioverter/defibrillators or external cardioversion may reset all models to the VVI mode and a bipolar ELITE II™ Model 7086 to unipolar pacing and sensing. If Model 7086 is implanted with IS-1 unipolar leads, polarity must remain unipolar to maintain output and sensing capability. Proper operation may also be affected by interference from certain electrical equipment. Any pacing system may fail due to random component or battery failures, lead-related problems, or eventual cell depletion.

SIDE EFFECTS: Possible side effects include, but may not be limited to, body rejection phenomena, muscle and nerve stimulation, infection, erosion of pacing system through skin, thrombosis related to venous leads, embolism, and cardiac tamponade.

See the technical manual for more detailed information.

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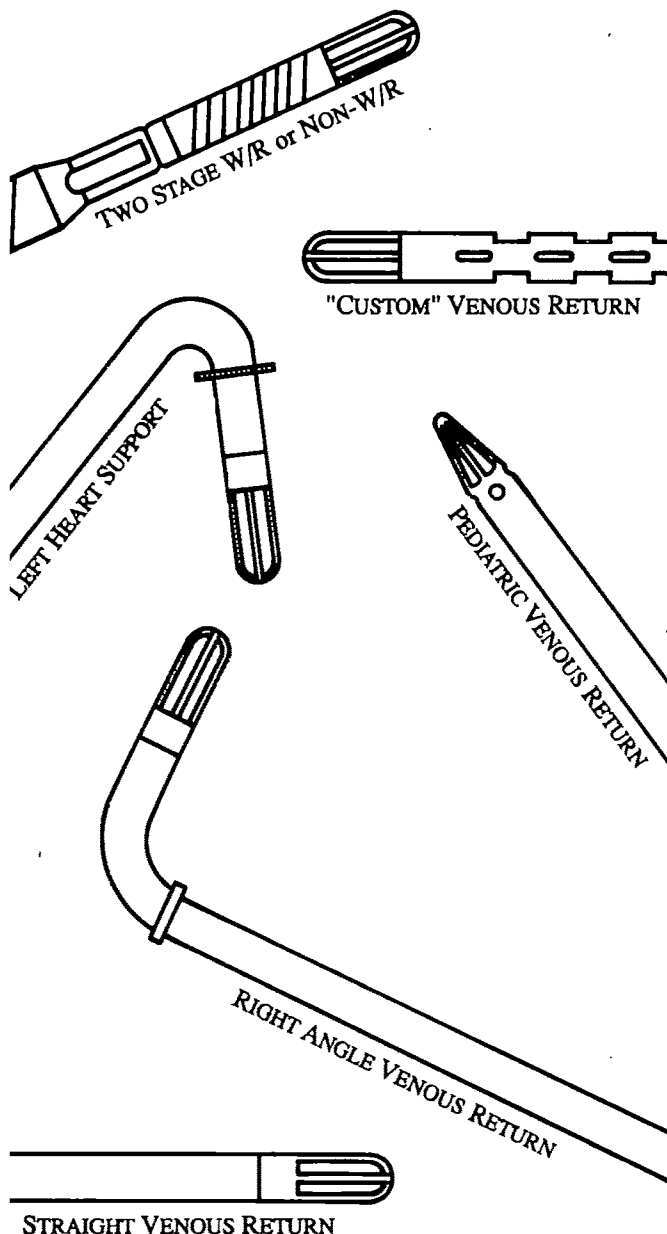
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As compared to other types of prostheses, preserved porcine bioprostheses exhibit certain potential advantages: the need for long-term anticoagulation may be minimized; and although the durability of porcine bioprostheses is a limiting factor in long-term evaluation, tissue degeneration is usually progressive and asymptomatic, thereby permitting detection with proper serial follow-up in persons with valvulopathy, and elective intervention when necessary.

Models 6625 LP and 6625-ESR *LP Mitral Carpenter-Edwards® Duraflex™ Bioprostheses are comprised of porcine aortic valves that have been preserved in buffered glutaraldehyde and then mounted on flexible frames. Glutaraldehyde is shown to both reduce the antigenicity of porcine aortic valves and increase tissue stability.

The frame is designed to be flexible at the orifice as well as at the commissures. The compliance of the stent's commissure supports is intended to reduce the loading shock at the valve commissures and free margin of the leaflets. The flexibility of the orifice is intended to reduce the loading shock at the base of the leaflet. The flexible orifice concept is based on the physiology and mechanics of natural heart valves and supported experience with implantation of excised homologous.

The lightweight frame is made of Elgiloy®, a corrosion-resistant alloy, chosen because of its superior spring efficiency and fatigue-resistant characteristics.

The metal frame is covered with a porous, leached polytetrafluoroethylene cloth to facilitate tissue ingrowth and encapsulation. The leaflet orifice is contoured to support the right coronary cusp of the porcine valve. The commissure supports are not equivalent to conform to the anatomical configuration of the porcine aortic valve. The stent ring has a soft, silicone-rubber insert that is covered with a porous, seamless polytetrafluoroethylene cloth. The compliant nature of the stent ring facilitates coaptation between the valve and an often irregular or calcific tissue bed.

The porcine aortic valves are fixed in buffered glutaraldehyde, and then mounted on cloth-covered frames. After mounting, the valves are tested *in vitro* to ascertain their competency and flow characteristics. After final inspection, the valves are sterilized, rinsed, and then transferred into fresh glutaraldehyde and packaged under aseptic conditions.

Low Pressure Fixation
In a study by Thomas, et al., advice that to maintain optimum mechanical properties in the fixed porcine aortic leaflet tissue, the full collagen waveform or crisp originally present in the relaxed leaflet tissue should be retained. In addition, these studies show that the collagen waveform is sensitive to alteration at fixation pressures as low as 4 mm Hg. Edwards CVS Division has developed a process to fix porcine aortic valves at a hydrostatic pressure less than 4 mm Hg to minimize alterations in the collagen waveform of the aortic valve tissue. Low pressure fixation of Carpenter-Edwards Duraflex™ bioprostheses is intended to increase the clinical durability of these valves; however, data regarding Carpenter-Edwards Duraflex™ bioprostheses are insufficient to demonstrate that durability has been increased by this preparation technique or that calcification has been reduced.

Indications
Bioprostheses are indicated for use in patients suffering from valvular heart disease. Mitral valvular heart disease is a condition involving any of the following: obstruction of the heart valve or stenosis; leakage of the valve, known as regurgitation or insufficiency; and combination of the two, sometimes referred to as mixed disease or combined lesions. Valvular heart disease may be caused by any number of factors, including congenital abnormalities, infection by various microorganisms, degenerative calcification, rheumatic heart disease, and rupture or dysfunction of the mitral subvalvular mechanism secondary to myocardial infarction.

Bioprostheses are used particularly in those patients for whom long-term anticoagulation is contraindicated or who may be difficult to maintain on anticoagulation therapy.

The Carpenter-Edwards Duraflex™ bioprostheses is intended for use in patients whose mitral valvular disease is sufficiently advanced to warrant replacement of their natural valve with a prosthesis. It is also intended for use in patients with a previously implanted mitral valve prosthesis which is no longer functioning adequately and requires replacement. In the latter case, the previously implanted prosthesis is surgically excised and replaced by the replacement prosthesis.

Warnings
For Single Patient Use Only

In the presence of conditions affecting calcium metabolism or when calcium containing chronic drug therapies are used, the use of a mechanical prosthesis as an alternative should be considered. This is also true in patients under 20 years of age, in patients on a high calcium diet, and in patients who are on antidiuretic hemodialysis.

The decision to use a tissue valve must ultimately be made by the physician on an individual basis after carefully evaluating the short- and long-term risks and benefits to the patient, and considering alternative methods of treatment. The overall durability, especially long-term, has not been established for bioprostheses.

Serious complications, sometimes leading to replacement of the valve and/or death, may be associated with the use of tissue valves (see Complications). A full explanation of the benefits and risks should be given to each prospective patient before surgery.

Note: Bioprostheses should be used with caution in the presence of severe systemic hypertension or when the anticipated patient longevity is longer than the known longevity of the prosthesis (See Clinical Experience).

Careful and continuous medical follow-up (at least annually by a visit to the physician) is advised so that valve-related complications, particularly those related to material failure, can be diagnosed and properly managed.

Replacement of prosthetic heart valves who are undergoing dental procedures should receive prophylactic antibiotic therapy to minimize the possibility of prosthetic infection.

Bioprosthetic heart valve recipients should be maintained on anticoagulant therapy, except where contraindicated, during the initial healing stages after implantation, approximately 2 to 3 months. Anticoagulants should then be discontinued over a period of 10 days, except in those patients for whom indefinite anticoagulant protection is indicated, i.e., in the absence of sinus rhythm and in patients with a dilated left atrium, calcification of the aortic wall or history of previous aortic thrombosis. Please refer to the most recent Clinical Experience attachment for data on anticoagulation relating to these valves. The appropriate anticoagulation therapy must be determined by the physician on an individual basis.

Adequate rinsing with physiological saline, as described in the Technique section, is mandatory before implantation to reduce the glutaraldehyde concentration. No other solutions, drugs, chemicals, antibiotics, etc. should ever be added to the glutaraldehyde or rinse solutions, as irreparable damage to the leaflet tissue, which may not be apparent under visual inspection, may result.

Carpenter-Edwards Duraflex™ bioprostheses must be kept moist at all times. Drying out will cause irreversible damage to the leaflet tissue. To prevent drying out during implantation, the valves should be irrigated periodically on both sides with sterile physiological saline.

Passing diagnostic catheters and transvenous pacing leads across Carpenter-Edwards® Duraflex™ bioprostheses could damage the valve. Consequently, it is recommended that these procedures be avoided.

Both the valve and glutaraldehyde storage solution are sterile. The outside of the jar is not sterile and must not be placed in a sterile field. Furthermore, the valve and container should never be subjected to sterilization procedures involving ethylene oxide, propylene oxide, steam, or irradiation.

Storage between 4°C (39°F) and 25°C (77°F) is recommended; however, care should be exercised to avoid freezing or extreme heat, which may damage the valvular tissue.

Glutaraldehyde may cause irritation of the skin, eyes, nose and throat, and may also cause skin sensitization. Avoid prolonged or repeated contact or prolonged breathing of the vapor. Use only with adequate ventilation. In the event of contact with the eyes, seek medical attention.

Surgical Precautions
The models 6625 LP and 6625-ESR *LP Duraflex™ mitral valves are unapproved for indications other than mitral valve replacement.

Complications

As with all prosthetic heart valves, serious complications, sometimes leading to death, may be associated with the use of these valves. In addition, complications due to individual patient reaction to an implanted device, or to physical or chemical changes in the components, particularly those of biological origin, may occur at varying intervals (hours or days) necessitating reoperation and replacement of the prosthetic device.

Complications associated with the use of Carpenter-Edwards Duraflex™ bioprostheses, compiled from the literature and from reports received through the computerized tracking system in accordance with the United States (Federal) regulations establishing Good Manufacturing Practices section 820.198, include stenosis, regurgitation through an incompetent valve, perivalvular leak, endocarditis, hemolysis, thromboembolism, thrombotic obstruction, bleeding related to the use of anticoagulant therapy, ventricular perforation by suture points, looped sutures, and malfunctions of the valve due to distortion at implant or physical or chemical deterioration of valve components. Types of tissue deterioration include infection, calcification, dislodging, perforation, suture erosion, instrument trauma, and leaflet or suture wall detachment from the valve suture points. These complications may present clinically as abnormal heart sounds, shortness of breath, exercise intolerance, dyspnea, orthopnea, ascites, fever, arrhythmias, hemorrhage, transient ischemic attack, stroke, paralysis, low cardiac output, pulmonary edema, congestive heart failure, cardiac failure, and myocardial infarction.

Note: Based on reports in the literature on tissue valves, there appears to be an increased incidence of leaflet calcification in patients under the age of 20. In this regard, animal research studies show that a high systemic calcium level can lead to early calcification. Furthermore, at least one published report describes a potential relationship between the consumption of dairy calcium supplements and early leaflet calcification in an adult. When feasible, repeated intravenous injections containing calcium should be avoided during the postoperative period, and excessive milk or dairy product consumption should be avoided in children. There are no clinical data presently available demonstrating increased resistance of Carpenter-Edwards Duraflex™ bioprostheses to calcification as compared to other commercially available porcine valves.

See package insert accompanying product for a full discussion of warnings, contraindications, complications and postoperative information.

Caution: Federal (USA) law restricts this device to sale by or on the order of a physician.

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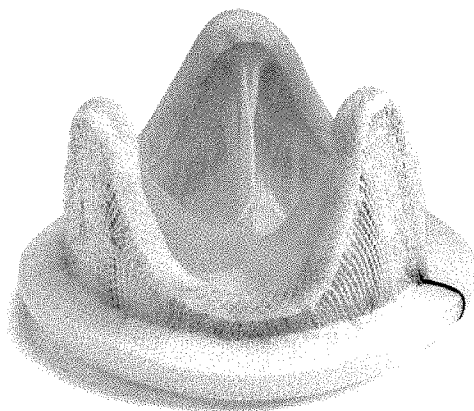
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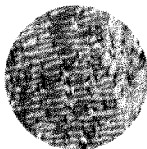
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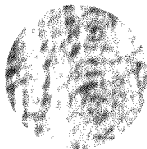
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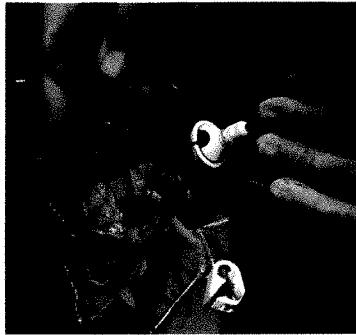
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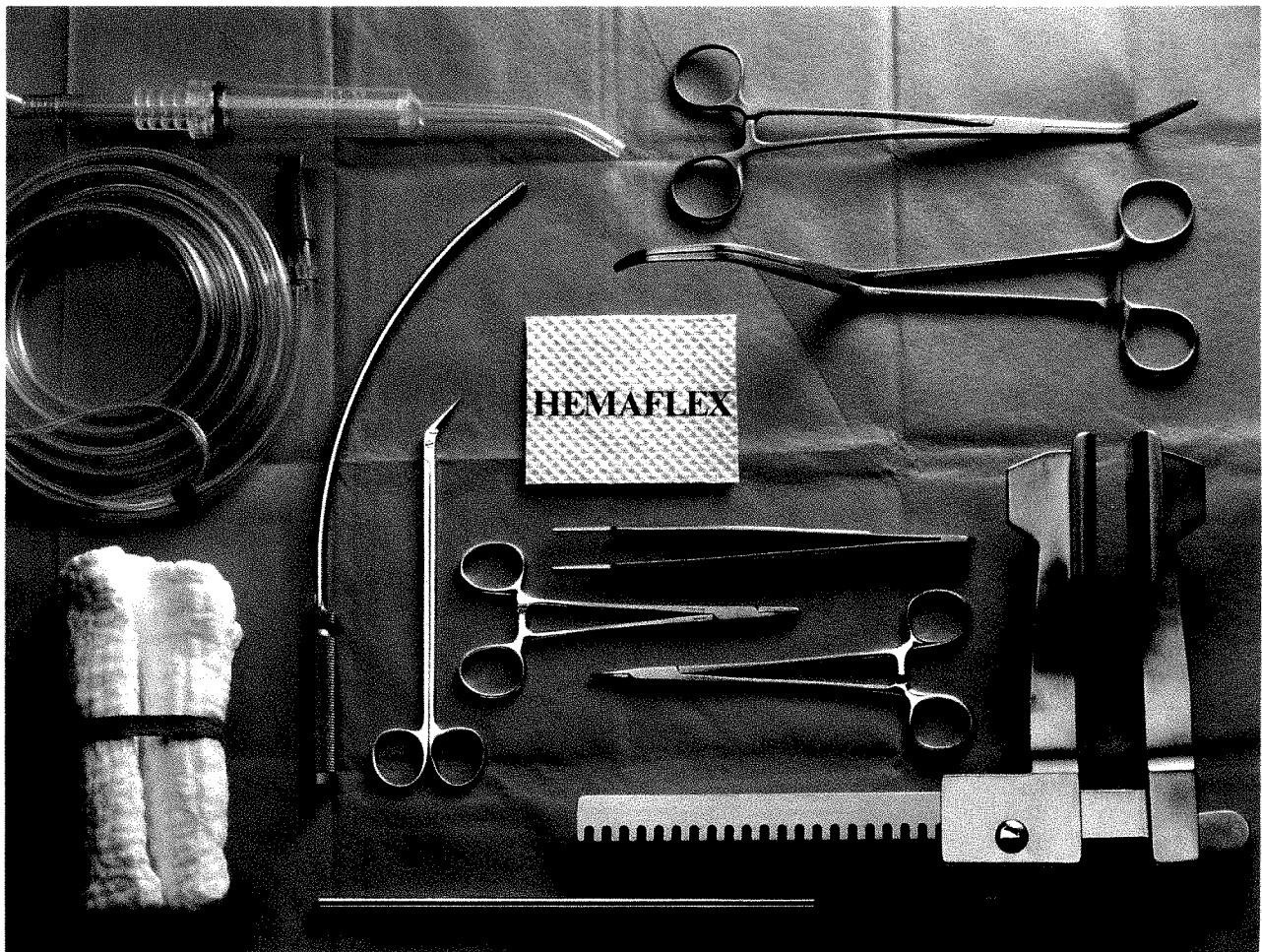
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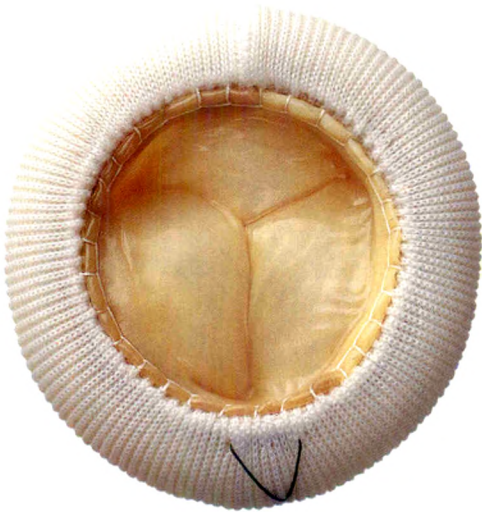


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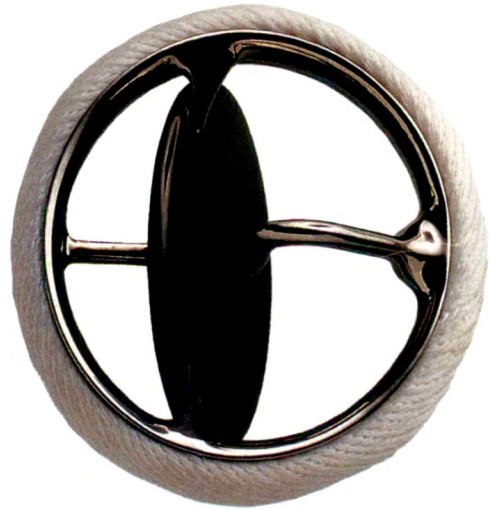
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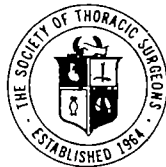


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The Annals of Thoracic Surgery publishes original papers on topics in thoracic and cardiovascular surgery. Also featured are case reports, "how to do it" articles, classics in thoracic surgery, collective and current reviews, correspondence, and book reviews. All manuscripts, correspondence, and editorial business should be sent to the above address. Guidelines for collective and current reviews are available on request.

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- ☐ Type manuscript double-spaced throughout (including title page, abstract, text, references, tables, and legends) on one side only on 22 × 28 cm (8½ × 11 inch) opaque bond paper with 3 cm (1¼ inch) margins all around. *This also applies to correspondence.* Type the last name of the first author in the upper right-hand corner of each page, including the title page.
- ☐ Arrange manuscript as follows: (1) title page, (2) abstract, (3) text, (4) references, (5) tables, and (6) legends. Number pages consecutively, beginning with the title page as page 1 and ending with the legend page.
- ☐ A manuscript for an *original article* ordinarily should not exceed 26 double-spaced typewritten pages, and should be proportionally shorter the more illustrations and tables that are included.
- ☐ The *text* for case reports should be *no more* than 4 double-spaced typewritten pages. If tables or illustrations are included, the text must be reduced. The text for a "how to do it" article should be even briefer, but with detailed illustrative material. Case reports and "how to do it" articles that exceed the allowable length will not be considered for publication.
- ☐ Referencing should be selective and pertain directly to the work being reported. Except in collective and current reviews, comprehensive listings serve no useful purpose and utilize valuable space. As a general guide, original articles

should have no more than 20 references; case reports, 8 references; and "how to do it" articles, 5 references.

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- ☐ Give the paper as short a title as possible. Also submit a short title of 3 or 4 words to be used as a running head. Include only the names of the authors directly affiliated with the work, stating for each the single highest academic degree. Include the name and location of no more than two institutional affiliations.
- ☐ If the paper has been or is to be presented at the annual meeting of The Society of Thoracic Surgeons, the Southern Thoracic Surgical Association, or another scientific organization, provide a footnote giving the name, location, and dates of the meeting.
- ☐ At the bottom of the page, type "Address reprint requests to Dr . . ." followed by the last name, exact postal address with zip code, *telephone number*, and *FAX number* of the author to whom communications, proofs, and requests for reprints should be sent.

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- ☐ Provide an abstract *no longer than 175 words* for an original article. Abstracts for case reports and "how to do it" articles should be shorter (50 to 75 words). An abstract must accompany *every* contribution, except for letters to the editor. Include several (3 to 5) keywords to assist in cross-indexing the article.

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- ☐ Generally, the text should be organized as follows: Introduction, Material and Methods, Results, and Comment.
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- ☐ Spell out, or define in parentheses, all abbreviations, even if they are commonly employed.
- ☐ Give all measurements and weights in *Système International (SI) units*. See "SI Unit Implementation—the Next Step" (JAMA 1988;260:73–6).
- ☐ For statistical nomenclature and data analysis, follow the "Guidelines for Data Reporting and Nomenclature" published in *The Annals of Thoracic Surgery* (1988;46:260–1) and found in the program book for the annual meeting of The Society of Thoracic Surgeons.
- ☐ Type footnotes at the bottom of the manuscript page on which they are cited. Credit suppliers of drugs, equipment, and other material described at length in the paper in footnotes, giving company name and location.
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(Continued)

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8. Grillo HC, Suen HC, Mathisen DJ, Wain JC. Resectional management of thyroid carcinoma invading the airway. *Ann Thorac Surg* 1992;54:3–10.
(List all authors if 6 or fewer; otherwise list first 3 and add “et al.”)

Chapter in Book

12. Vouhé PR. Transplantation of thoracic organs in children. In: Fallis JC, Filler RM, Lemoine G, eds. *Pediatric thoracic surgery*. New York: Elsevier, 1991:319–29.

Book (Personal Authors or Editors)

18. Shields TW, ed. *Mediastinal surgery*. Philadelphia: Lea & Febiger, 1991:1–10.

Tables

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■ One Hundred Thirteenth Annual Meeting of the American Surgical Association, Baltimore, Maryland—April 1-3, 1993

For information on this meeting, contact American Surgical Association, Department of Surgery, CB 7245, University of North Carolina, 136 Burnett-Womack Building, Chapel Hill, NC 27599; or telephone (919) 966-4320 (facsimile: (919) 966-6009).

■ Thirteenth Annual Meeting of the International Society for Heart and Lung Transplantation, Boca Raton, Florida—April 1-3, 1993

For information on this meeting, contact ISHLT Headquarters, 435 Michigan Ave, Suite 1717, Chicago, IL 60611; or telephone (312) 644-0828.

■ American College of Surgeons, Montreal, Canada—April 25-28, 1993

For information on this meeting, contact American College of Surgeons, 55 E Erie St, Chicago, IL 60611; or telephone (312) 664-4050 (facsimile: (312) 440-7014).

■ Seventy-third Annual Meeting of the American Association for Thoracic Surgery, Chicago, Illinois—April 26-28, 1993

For information on this meeting, contact American Association for

Thoracic Surgery, 13 Elm St, Manchester, MA 01944; or telephone (508) 526-8330 (facsimile: (508) 526-4018).

■ Fourteenth Annual Scientific Session of the North American Society of Pacing and Electrophysiology, San Diego, California—May 6-8, 1993

For information on this meeting, contact NASPE, 377 Elliot St, Newton Upper Falls, MA 02164; or telephone (617) 244-7300 (facsimile: (617) 244-3920).

■ 1993 World Symposium on Cardiomyoplasty and Biomechanical Assist, Paris, France—May 24-26, 1993

For information on this meeting, contact Beverly Farrier, ProMedica International, 620 Newport Center Dr, Suite 575, Newport Beach, CA 92660; or telephone (714) 640-5870, extension 22 (facsimile: (714) 759-6911).

■ International Symposium—Update in Cardiac Surgery, Coimbra, Portugal—May 28-29, 1993

For information on this meeting, contact Prof M. Antunes, Cirurgia Cardioracica, Hospital da Universidade, 3000 Coimbra, Portugal; or send facsimile to 351-39-29674.

■ The Society of Thoracic Surgeons/Duke University Medical Center: Surgery for Coronary Artery Disease, Durham, North Carolina—June 4-6, 1993

For information on this course, contact Vanessa Moore, PO Box 2986, Duke University Medical Center, Durham, NC 27710, (919) 684-6077; or The Society of Thoracic Surgeons, Surgery for Coronary Artery Dis-

ease, 401 N Michigan Ave, Chicago, IL 60611-4267, (312) 644-6610.

■ The International Society for Cardiovascular Surgery/The Society for Vascular Surgery, Washington, DC—June 7-9, 1993

For information on this meeting, contact the Association offices, 13 Elm St, Manchester, MA 01944; or telephone (508) 526-8330 (facsimile: (508) 526-4018).

■ Fifth European Congress on Extra-Corporeal Circulation Technology, Arles, France—June 9-12, 1993

For information on this meeting, contact MOBO Promotions/FECECT, Catharijnesingel 105, 3511 GV Utrecht, Netherlands; or telephone 31-(0)30-310751 (facsimile: 31-(0)30-311198).

■ World Congress on Diseases of the Chest, Amsterdam, the Netherlands—June 13-18, 1993

For information on this meeting, contact XVII World Congress on Diseases of the Chest, International Academy of Chest Physicians & Surgeons, 3300 Dundee Rd, Northbrook, IL 60062-2348.

■ Nineteenth Annual Meeting of The Western Thoracic Surgical Association, Carlsbad, California—June 24-26, 1993

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■ Le Club Mitrale, Paris, France—June 26-June 3, 1993

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■ **Ninth Congress of the International Society for Artificial Organs, Amsterdam, The Netherlands—July 4-8, 1993**

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■ **Twenty-first World Congress of The International Society for Cardiovascular Surgery, Lisbon, Portugal—September 12-15, 1993**

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■ **Seventh Annual Meeting of The European Association for Cardio-Thoracic Surgery, Barcelona, Spain—September 20-22, 1993**

For information on this meeting, contact EACTS Executive Secretariat,

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■ **Neurological Injury and Pediatric Cardiac Surgery (including results of the prospective Boston Circulatory Arrest Study), Boston, Massachusetts—September 30-October 2, 1993**

For information on this meeting, contact Laura Young, Department of Cardiac Surgery, Children's Hospital, 300 Longwood Ave, Boston, MA 02115; or telephone (617) 735-7930 (facsimile: (617) 735-6742).

■ **Fifty-ninth Annual Scientific Assembly, American College of Chest Physicians, Orlando, Florida—October 24-28, 1993**

For information on this meeting, contact American College of Chest Physicians, 3300 Dundee Rd, Northbrook, IL 60062; or telephone (708) 498-1400 (facsimile: (708) 498-5460).

■ **Fortieth Annual Meeting of the Southern Thoracic Surgical Association, Panama City Beach, Florida—November 4-6, 1993**

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■ **Sixty-sixth Scientific Session of the American Heart Association, Atlanta, Georgia—November 8-11, 1993**

For information on this meeting, contact American Heart Association, 7320 Greenville Ave, Dallas, TX 75231; or telephone (214) 373-6300 (facsimile: (214) 373-3406).

■ **Thirtieth Annual Meeting of The Society of Thoracic Surgeons, New Orleans, Louisiana—January 31-February 2, 1994**

For information on this meeting, contact Richard P. Anderson, MD, The Society of Thoracic Surgeons, 401 N Michigan Ave, Chicago, IL 60611; or telephone (312) 644-6610 (facsimile: (312) 527-6635).

■ **Forty-third Annual Meeting of the American College of Cardiology, Atlanta, Georgia—March 13-17, 1994**

For information on this meeting, contact American College of Cardiology, 9111 Old Georgetown Rd, Bethesda, MD 20814; or telephone (800) 253-4636.

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Ben P. Bidstrup, FRACS, Judy Harrison, MB, David Royston, FFARCS, Kenneth M. Taylor, FRCS, and Tom Treasure, FRCS

■ Blood and Albumin Cardioplegia Preserve Endothelium-Dependent Microvascular Responses

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■ Effect of Vascular Clamp on Endothelial Integrity of the Internal Mammary Artery

James Kuo, FRCS, Keith Ramstead, FRCS, Vehid Salih, MSc, Adam Coumbe, MRCPATH, Timothy R. Graham, FRCS, and C. Terence Lewis, FRCS

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■ High-Risk Cardiac Operation: A Viable Alternative to Heart Transplantation

Maryl R. Johnson, MD, Maria Rosa Costanzo-Nordin, MD, Alain L. Heroux, MD, Walter G. Kao, MD, G. Martin Mullen, MD, Roque Pifarré, MD, and Henry J. Sullivan, MD

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Szabolcs Szentpetery, MD, Crile Crisler, MD, and George L. B. Grinnan, MD

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Koichi Tabayashi, MD, Koki Niibori, MD, Atsuchi Iguchi, MD,

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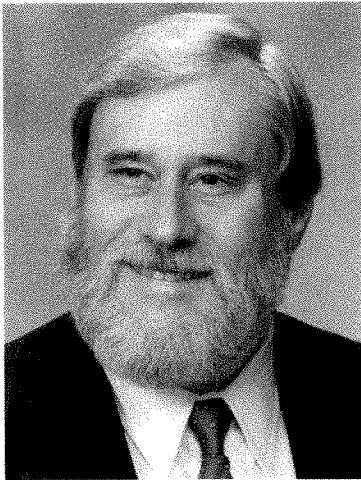
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Unsocialized Medicine: The Decline of Surgical Collegiality

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Fellow members and guests. Let me first express my gratitude for the honor you have paid me in allowing me to be your president. It is the apex of my medical career. I also want to thank all who have contributed to making the 39th Annual Meeting of the Southern Thoracic Surgical Association a success: the Postgraduate and Program Committees, the authors, in particular Dr Baue for his wonderful presentation on multiple organ dysfunction and Dr Naef for his glimpse into our past and future, and finally the executive staff.

Election to the Presidency of an organization is thrilling in direct proportion to one's respect for the organization, and, paradoxically, humbling in equal measure. Because the Southern Thoracic Surgical Association was my first love and continuing favorite, you will realize how elated I was to be chosen. In the reflection that followed I began to wonder at the course that took me from a small mill town in north-central Wisconsin to the podium of this great organization. Ultimately the route seemed related to the end and therefore worthy of consideration, but mostly it seemed pertinent to the topic of surgical collegiality that I have chosen as the topic of this address.

This address is not designed to actuate and therefore is not an oration. Rather it is designed to promote reflection,

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by an informal stringing together of ideas to see what happens. This is defined as an essay by Dr O. B. Hardison in his essay on the essay [1]. That is, it is a trial or test of ideas. The form is uniquely appropriate to our times. The first and greatest essayist, and author of the term, was Michel de Montaigne. He sent forth his first collection in 1580, into a world turned chaotic by the Reformation and still stunned by the ferocity of the St. Bartholomew's Day Massacre, just eight years before. He said that he sought a calmness and a detachment he called *Ataraxy* to follow an inward questioning. His motto was "What Do I Know."

One thing I know is the path I have taken. My family was my earliest influence. To paraphrase the opening lines of Norman Maclean's wonderful book *A River Runs Through It* [2], in our family there was no clear line between religion, fly fishing (Fig 1), and dentistry (Fig 2). Like Reverend Maclean, my father (Fig 3) used the word *beautiful* as a natural form of speech. It was applied equally to a well-cast fly, a perfect gold inlay, and his favorite hymns. It was a paradox in a man so tough at the core. It led my sister, my brother, and me to an early recognition of the intrinsic worth of a thing well done.

My mother (Fig 4) created in us an unquenchable curiosity about every aspect of life; about music and art, literature and nature, and people, all carried along by her own bright intellect and informed by her sense of social justice.

The physicians in my hometown could well have been selected as role models. They were caring and kindly, intelligent and involved, and they actually talked to kids. Because I was sick with histoplasmosis for a few years and had a lot of contact with them it is easy to see why I always wanted to be a doctor. Getting there was a rather undistinguished process.

My surgical training was provided by a number of outstanding surgeons, some of whom I wish to present. Doctor Fiorindo Simeone (Fig 5) was my Chief of Surgery. He quickly gave us interns to understand the responsibility of a surgeon with the observations: "When one man allows another to assail his body with stainless steel, they have established a life-long contract," and, "We have much to learn from our patients but must never forget how dearly they pay for our tuition." Coupled with his demanding sternness was a boundless intellectual bent. He once told me, in awe, that the thing that impressed him most in his career was the time Dr Edward Churchill showed him two whole file drawers full of papers he was working on. He himself introduced to surgery Lewis Carroll's concept expressed by the Red Queen that only



Fig 1. A. R. Cook with trout.

by out-distancing ourselves do we uncover new problems [3]. This image was applied to the recognition of shock-lung in Vietnam military casualties so badly injured they would have died on the field in prior wars.

In 1960 Dr Simeone arranged for me to spend a year with his old friend Prof John Kinmonth (Fig 6) at St. Thomas' Hospital in London. This remarkable man accepted a pea-green foreign resident in his newly formed cardiac surgery unit as if he were a member of the royal family and provided me with the opportunity to perform, analyze, and report my first scientific research. He also



Fig 2. A. R. Cook with drill.



Fig 3. Arthur R. Cook, DDS.

took me to the theater and for a ride in his Morgan 2+2. On my return he was so gracious and involved as to write to Dr George Clowes and suggest that thoracic surgery might be a good field for me to pursue.

There was no saying no to Dr Clowes (Fig 7), and thus I was recruited to one of the most exciting clinical research units in the country. We had the first Engstrom volume ventilator and Siggard Anderson rapid blood-gas analyzer in America, the first membrane oxygenator, and, thanks to Dr Louis Del Guercio, the first bedside cardiac output equipment. Due to Dr Clowes' insatiable scientific curiosity, patients with every conceivable disease process were studied. This experience created a physiologic underpinning for all my subsequent surgical life. When I announced that I was taking this treasure back to Wisconsin, he said "no, you're not, you're going to Montreal with me to meet Dr Webb." That is how I got my first job.

Watts Webb (Fig 8) is a consummate master of conceiving, conducting, polishing, and funding thoracic surgical research, and he gave his all to show me how. Our clinical and laboratory research covered a wide variety of sub-



Fig 4. Laura C. Cook.



Fig 5. Fiorindo A. Simeone, MD.

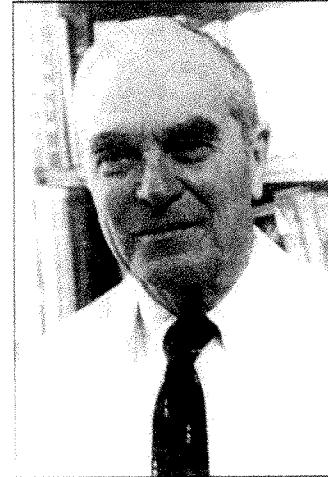


Fig 7. George H. A. Clowes, MD.

jects, so much so that after presenting my first paper to this association in 1965 on some adverse effects of smoking and my next on the adverse effects of alcohol, several senior members threatened not to accept any more papers from us for fear we would find something fundamentally wrong with sex.

Finally, while in Dallas, I had the privilege of working with Dr Robert Shaw (Fig 9). His gift for perceiving the practical good that thoracic surgery can do was epitomized in a case he asked me to assist him with, in which transthoracic drainage and grafting of a Pott's abscess reversed a paraplegia of 48 days' duration. A year later I had done some other transthoracic spinal cases when he wrote from Afghanistan to offer two of his Afghani cases and the proposal that I write them all up to call attention to the procedure in the American literature.

This has been a lengthy description of what for most of my generation was a common experience. I give it to make two points. First, note the high degree of personal involvement of my mentors. They never sent me to a

meeting, they took me, and introduced me to their friends. Second is the enormous variety of clinical and research experience to which I was exposed along the way. This clinical and laboratory experience was associated with a high degree of socialization. I do not think this occurs commonly today. Those men, and others too numerous to mention, were also eager that we share their involvement with their colleagues in everyday interchange, and particularly with their organizations. Many of those men are in this room today.

Dallas was a good example. Doctors Paulson and Shaw made rounds on the wards at Parkland Hospital each Saturday morning, and this was followed by a mortality conference. Imagine, if you can, Robert Shaw, Don Paulson, Maurice Adam, Milton Davis, Hugh Wilson, Watts Webb, Hal Urschel, Bill Ashe, Paul Ellis, John Kee, Tom McSwain, and Eldon Sieble all in one room defending their clinical decisions. Talk about discussion; we should have had our own Osler Abbot award. No one had to be prompted to attend. No one would have missed it. We



Fig 6. Professor John B. Kinmonth.

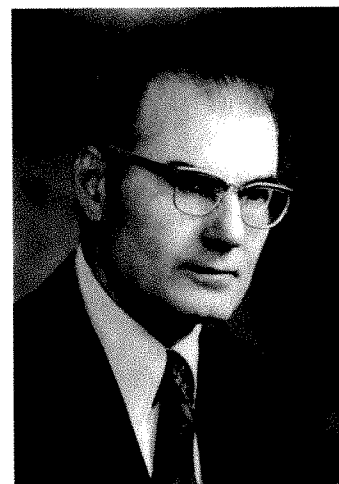


Fig 8. Watts R. Webb, MD.



Fig 9. Robert R. Shaw, MD.

had one twentieth of the 1966 membership of this association, possibly the loudest twentieth, but looking at the roster for that year I suspect that members from Nashville, Memphis, and Atlanta were sharing the experience.

Collegiality, scientific interchange, and fun all happened at once and I was thrilled to be part of it. Imagine my delight when I went with Dr Webb to Freeport to deliver the infamous smoking paper and discovered the same mix in the Southern Thoracic Surgical Association. I fell in love with this organization, and I am happy to say my love affair continues unabated after 27 years. The catalogue of brilliant scientific information, close personal friendships, riotous laughter, and unadulterated mischief provided by this organization are among my brightest memories. Sadly, this has not been everyone's experience.

During the past year I have attempted to collect some history of the organization and also the demographics of attendance at the meetings. Due to fading memories, incomplete Association records, and simple disinterest, these demographics are flawed, but, still, certain patterns emerge. The most striking and unusual is that looking at each yearly group of new members between 3 and 6 people begin to attend regularly and then never stop. The founding of The Society of Thoracic Surgeons did not affect attendance at this meeting. This is true of recent years as well as the early years. From this group have come all of your officers and committee members, and many of the finest scientific presentations. Clearly, for them the organization provided exactly the role for which it was founded.

Equally clearly, it has not done so for the greater proportion of members. More than 500 members have attended two meetings or less. It is this group with which I am concerned. After a year of contemplation the question for me remains, How did the organization fail these people or they it? Before the study was complete I had thought it was a phenomenon of the younger members, but that is not true. It was equally noted in the founder's group.

Here I should put forward the impetus for this address. I belong to many medical organizations ranging from the most general to the most specialized and local. A common disease affects many of these organizations. They are becoming senile and in some cases dying. In the time I have been in Massachusetts I have seen the demise of the Surgical Section of the Massachusetts Medical Society. It was founded before the Revolutionary War, and its history was rich with famous men and their deeds. There has been a simultaneous decrease in attendance and shift to older members in the Massachusetts Chapter of the American College of Surgeons. This was once the largest and most active chapter in the United States. Please recognize that I take what happens to my organizations personally. This decline appears not to be a phenomenon limited to medicine. Patients tell me the same thing is happening in the service organizations, the Masonic Lodge, and the Knights of Columbus. What is behind this decline in collegiality and socialization, how might it affect the Southern Thoracic Surgical Association, and what if anything can be done about it?

The historical material I solicited from the members was filled with letters, slides, articles, and lots of memories. Strangely, few if any dealt with the scientific content of the meetings. Almost all recalled the fun, the people, and the places. However, one member responded, "who cares, why dwell on the past?" This would seem an easy question to answer but in fact requires our consideration. A medical student who is on a committee with me said, "Much of the thrust of current meetings seems to be how to recapture medicine as it was. It will never again be as it was. We want to go to meetings that deal with our realities." What are those realities, and what is the process in which we find ourselves?

It should be clear from my earlier remarks what I thought medicine should be like. Now, with many of my contemporaries, I am caught in a frustrated grieving for the loss of my youthful altruism and expectations. This process has gone from early denial to anger and thence to resigned acceptance. On the way it has definitely permeated our contemporary discourse.

For one example, in 1965 we began to deal with Medicare and Medicaid and their erosion of the doctor/patient relationship. Medicaid in particular began under an evil star. It was an outgrowth of the deceptive American myth that nothing is of value if it is not expensive and has driven the cost of medical care to cosmic levels. In addition, at a single stroke it negated and demeaned a 200-year-old tradition of free medical care, of which we were justifiably proud, and effectively prevented us from giving it. Now 35 million Americans do not have medical insurance and we are blamed for it. Well, a few years ago my office medical assistant analyzed my billing costs for Medicaid patients and found they were greater than collections. So we instituted a policy of free care, which avoided billing them. The bureaucrats told us we could not do that because it undermined the system. Did I have anger and denial—you bet. Did I have acceptance—not yet.

In his presidential address to the Massachusetts Chap-

ter of the American College of Surgeons Dr Stuart Strong noted that these pressures have caused the subjects discussed at meetings to reflect anxiety and grief and to deal with the intrusion of external forces in our practices [4], and to shift organizational behavior toward economic goals. By belonging to these organizations we are tacitly drawn into this dialogue instead of maintaining an individual ethicism in which the patient and his or her care are our primary consideration. Young surgeons, saddled with enormous debt at the end of training, feel these same pressures even more strongly than we do, and for many this is a source of embarrassment. Clearly they do not want to belong to an organization that underlines the least altruistic areas of their life.

Well, the good news is that the entire 1992 meeting of the Massachusetts Chapter was spent on laparoscopic surgery with no discussion of any politically centered issues. We had the largest attendance and youngest group in nearly a decade. In a letter to the Editor of the *Journal of the American Medical Association*, Dr Bernstein of the Boston University School of Medicine notes that a study of their graduates from 1986 to 1990 showed no association between debt and choice of a highly paid specialty and that this corroborated the Graduate Questionnaire of the Association of American Medical Colleges [5]. Doctor Strong went on to reflect that we could not assume that our medical mentors were totally happy with their choice and experience of medicine. Yet they usually exuded pleasure, interest, and energy in its practice, and close personal contact with their trainees.

Earlier this year Dr Waldhausen, reflecting on the history of the American Association for Thoracic Surgery and the Snowbird Conference on Cardio-Thoracic Surgical Training, brought home some of these factors with great force [6]. He said, "For an association to remain viable and to fulfill its purpose, its members must not look only on the glorious past. They, and particularly the younger generation, must look to the future and at the challenges that face us." He noted further that "We must face the fact that our specialty in many regards has been shrinking; that thoracic surgeons introduced cardiac catheterization, pediatric cardiac surgery, critical care units, and support for cardiogenic shock and that in these and many other areas we have retreated completely, and in others are hardly visible." He states, "We have, in part, lost our way. We no longer participate in total care of our patients. Too often we have become OR technicians and are forcing our residents into a similar mold." Possibly this is a mold they do not want and of which they cannot be proud.

Doctor Anderson, in his presidential address to the Western Thoracic Surgical Association, also enumerated the many changes in thoracic and cardiovascular surgery and pointed out how interrelated they were with broader social changes [7]. Certainly our younger members have been subject to all these medical and societal pressures. You may have noticed that the winds of change seem to be piping up.

I believe we are not only in a period of gradual change. We are in a period of upheaval. We are not only the

passive victims of change. We ourselves are fomenting it. The recent Presidential election makes that manifestly clear. This societal upheaval spreads across every facet of contemporary life. In a recent issue of his column "This View of Life" Stephen Jay Gould reflects on the parallels between his theory of punctuated equilibrium in evolutionary biology and the observations of columnist David Warsh [8]. Mr Warsh was commenting on theories of punctuated equilibrium in social science put forth by Karl Marx. Having just been to Russia and experienced the chaos that has accompanied the fall of communism, Dr Gould states that "Russia is presently in the midst of a punctuation that must soon resolve itself one way or another into some form of promise or prosperity, or some species of chaos and dissolution." He further notes Mr Warsh's argument that gradualism is being challenged across a broad range of human activity: the introduction of quantum theory in physics, Thomas Kuhn's punctuational theory of the history of scientific ideas, and chaos theory in mathematics.

He then states that modern punctualism emphasizes contingency. This may provoke more anxiety due to its unpredictable outcome, but embodies more hope in the power of people to control their future. He concludes, "You can't think much about future stabilities when you must struggle to put food on the table." That struggle is best buoyed by a good sense of humor such as that seen in the current version of Russian nesting dolls. A big Yeltsin is on the outside and inside, first Gorbachev then Brezhnev, Khrushchev, and Stalin, and finally a tiny Lenin at the core.

In a recent article dealing with contemporary American intellectual life and entitled "The Cultural Wars," the philosopher Daniel Bell takes note of the "rancorous cultural war . . . over the questions of multiculturalism, political correctness, the canon and deconstructionism" taking place in American universities [9]. This has raged most publicly in the controversy over core curricula in the humanities and spilled over recently in the press. The *New York Times* for October 10th noted that the classics reading list at Columbia was being changed for the first time since the beginning of the century. The product of 3,000 years of Western thought is being casually dismissed as the politically incorrect product of DWEMs—Dead White European Males. Bell further notes that "there is no broad intellectual life and no broad intellectual public today," and that "specialization has led to an intellectual parochialism that ignores all cultural considerations outside its own narrow sphere."

Looking at the future he sees "the persistent problems of poverty and racial tension, . . . the unraveling of the middle class, . . . the erosion of its comfortable expectations," and "the possibility that this may be the first generation in American history that will leave its children poorer than itself." Added to that bleak picture he notes the loss of a cohesive utopian, universalist philosophy present since the age of enlightenment. This has been replaced in the West by a cultural nihilism and outside the West by a resurgence of Islamic fundamentalism that challenges all the values of the West.

He concludes, "All these create different sounds and furies and different kinds of cultural wars. We may be at the end of old ideologies and old history, but there are no unified sets of beliefs to take their place, only the splintering of cultures and political fragmentation."

These combined confusions of basic cultural tenets, modern American life, American medical politics, and thoracic surgical training are the heritage we give our younger members. Is it any wonder they are not particularly interested in further political discussions and deeply enjoy the structured peace of the operating room? Is it any wonder they question the relevance of the organizations so dear to us older members?

I believe there are answers to these confusions and would note that after every historical period of great turmoil there has been a giant leap forward in the basic human condition. We are in such a period now and must do all we can to bring our profession, our specialty, our organizations, and our young members to that brighter day.

What are our resources? Let us share a little folk wisdom with Gladys Knight and the Pips [10]. First she says, "Everybody's talking about the good old days, the good old days, the good old days. Well, let's talk about the good old days. Come to think of it, as bad as we think they are these will become the good old days for our children."* Then she sings, "for it's the laughter we will remember, as long as we remember the way we were."† She could certainly have been singing about the Southern Thoracic Surgical Association or, equally, the Russian nesting dolls. Laughter has always been an essential part of our organization, and we should be careful to nurture it. People in this room have recalled the laughter of 40 years ago. It is the music of the soul.

As noted before, we are embattled on many fronts. In seeking stability we might consider the embattled little Ukrainian village of Anatevka and the family of Tevye the dairy-man [11]. He says, "In our little village everyone of us is a fiddler on the roof trying to scratch out a pleasant, simple tune without breaking his neck . . . And how do we keep our balance . . . Tradition! Because of our tradition everyone here knows who he is and what God expects him to do . . . Without our tradition our life would be as shaky as a fiddler on the roof."‡ Tradition? Have we got tradition! Thirty-three years of recognizing pompous discussion with the Osler Abbot Award. Twenty-nine years of slide perfection ensured by the scourge of the Tiki Award. Do we have golf? We have Jim Brooks, who is reputed to have invented the game. Do we have history? We have Hawley Siler, whose first historical notes were impressed with a stylus on a block of clay

dredged up from Tampa Bay, back when a good cigar was a smoke. Yes, we have tradition.

But most important, we have mentors. I should know. I have been mentored by half the men in this room; encouraged, advised, befriended, criticized, restrained, promoted, and complimented. That, I have come to believe, is our greatest intrinsic strength. We know how to advocate for a younger surgeon, and all we need is just to do it! Here is the answer to "why look back?" Because in looking back we discover the richness of our history, the stability of our traditions, the value of our laughter, and the power of mentorship to lead our young members into the next 40 years. Looking at the bright new faces among us I see the opportunity to show them the pleasures of collegiality.

Another, unstated, question was "why participate?" That answer was provided by Theodore Roosevelt. He said, "Every man owes a part of his time and money to the business or industry in which he is engaged. No man has a moral right to withhold his support from an organization that is striving to improve conditions within his sphere."

Let me return momentarily to Stephen Gould. In a discussion of the conflict between moderns and classicists he recalls Jonathan Swift's satire of 1704 [12]. This was entitled *A Full and True Account of the Battle Fought Last Friday Between the Ancient and the Modern Books in St. James's Library*. The actual battle is introduced by a dispute between a spider (the moderns) and a bee (the ancients). Pointing to his web, the spider notes its mathematical purity and originality and accuses the bee of being able to create nothing new but only to forage among the ancient flowers. The bee responds, "I borrow but cause no harm in so doing, and I transmute what I borrow into new objects of great beauty and utility—honey and wax. But you, while claiming to build only from your own innards, must still destroy a hecatomb of flies for the raw material. Moreover, your vaunted web is weak, temporary, and ephemeral, whatever its supposed mathematical beauty (while the distillation of ancient knowledge endures forever) . . . How can you claim virtue for a product . . . based on your own gall?" The answer to this debate Gould suggests lies in an epigram of Edmund Burke: "All government—indeed, every human benefit and enjoyment, every virtue and every prudent act—is founded on compromise and barter." Professor Gould notes further "if we cannot talk we cannot bargain, compromise, and understand," and sadly notes that "I can no longer cite the most common lines from Shakespeare or the Bible in class and hold any hope of majority recognition. I am troubled that the primary lingua franca of shared culture may now be rock music of the last decade." He concludes with the words of the bee, "Whatever we have got, has been by infinite labor, and search, and ranging through every corner of nature: the difference is, that instead of dirt and poison, we have rather chosen to fill our hives with honey and wax, thus furnishing mankind with the two noblest of things, which are sweetness and light." So may it be with thoracic surgery and our part in it.

On my office wall there is a picture that I have come to

* Written for Gladys Knight and the Pips by Corky Guercio. Reprinted by permission.

† "The Way We Were" by Alan Bergman, Marilyn Bergman, and Marvin Hamlisch. © 1973 COLGEMS-EMI MUSIC INC. All rights reserved/international copyright secured/used by permission.

‡ Material from *Fiddler on the Roof* used by permission. © 1964 Joseph Stein, Mayerling Productions, Ltd, and Jerry Bock. Copyright renewed 1993 Joseph Stein, Mayerling Productions, Ltd, and Jerry Bock.

see as a perfect allegory for thoracic surgery today. It is a print of Winslow Homer's painting "Eight Bells." In the foreground are two mariners taking a noon-sight to fix their position by celestial navigation. A brassy light reflects from their wet oilskins as a pale sun just breaks through a storm-wracked sky. Around the ship is a tempestuous running sea. Beside them are the sturdy shrouds of a well-found sailing ship. Each man has a sextant. One is shooting the sun. The other is reading his instrument. They will compare readings for accuracy. Probably one is the captain and the other a young man learning his craft.

What is striking is that there, in the midst of the storm, these two hard-case sailors are performing a technical task that requires great skill and upon which the safety of their ship depends. By their attention to the work at hand they have created an island of calm totally detached from the forces around them. They cannot escape the sea and its storms; it is their life. But, confident of their ability and their ship, they are secure.

How closely this parallels the young surgeon and his or her mentor at the operating table, calmly performing a highly precise act despite the storm of disease and confusion in their patient, their specialty, and their world. What is being passed along is confidence and calmness in the face of adversity, what Michel Montaigne called *Ataraxy* and Sir William Osler called *Equinimitas*. When that mentorship is appropriately given and received a bond is formed that neither will wish to break. This is equally true in a surgical association.

As I look across this sea of faces, I recognize many grizzled captains of our craft and also the bright young apprentices eager to assume their roles. I am certain we have the traditions, good will, humor, ability, and confidence to pilot the Southern Thoracic Surgical Association through all the storms ahead.

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Measurement of Total DNA to Assess Lung Cancers

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Can DNA ploidy alone be used to discriminate between metastases and second primary neoplasms?

Ichinose and associates [1] suggest that difference in DNA ploidy as measured by flow cytometry can be used as a criterion by which to distinguish between second primary lung adenosquamous carcinomas and metastases from a primary neoplasm. This contention is an example of a general problem, and therefore it deserves close scrutiny.

By their own criteria, Ichinose and associates state that primary adenosquamous carcinoma of the lung occurs at a low frequency (2%). Because this is such an uncommon tumor, on statistical grounds alone, one must question the frequency with which a *second* primary adenosquamous cancer of the lung could be expected to occur. This consideration alone may make the results of their study questionable.

The weakness of flow cytometry as a method for detecting low-frequency aneuploid clones was not addressed by Ichinose and associates. In alleged second primary tumors, in which the ploidy of the second clone appears to differ from the ploidy in the initial primary tumor, it is possible that the second clone was present in

as quantifiable deviations in DNA ploidy. In such instances, it is entirely possible that the new metastasizing clones might have altered ploidy; ie, a primary tumor, itself diploid, may have given rise to aneuploid and hyperploid metastases. To judge the second (metastatic) tumor as a second primary tumor on the basis of ploidy alone would be of serious conceptual question.

Cytometric estimates of DNA ploidy determine only the total quantity of cellular DNA, and not the presence of specific chromosomes. Thus, cells from a patient who has ordinary chronic granulocytic leukemia with the Philadelphia chromosome (Ph') translocation would be measured as diploid, whereas cells from the same patient in blast crisis (in which additional chromosomal changes may have been acquired) would be measured as aneuploid by flow cytometry, although they retained the specific Ph' defect that indicates the origin of the disease. Because DNA ploidy studies by flow cytometry are incapable of detecting chromosomal rearrangements, by the criteria of Ichinose and associates such a patient would be considered as having two diseases when, in fact, there were two phases of a single disease.

A technical concern about the application of flow cytometry to tumor analysis has previously been discussed by us [5]. Flow cytometry is susceptible to loss of fragile cells or nuclei because of the need to prepare suspensions by enzymatic or mechanical methods. Thus, many poorly nourished and partially degenerated tumor cell nuclei may be lost during suspension preparation, and surface sampling of archival tumor specimen blocks for flow studies often miss areas that are deep to the surface. Ichinose and associates sampled the surfaces and *selected* well-preserved areas, and thereby they introduced the possibility of real bias. The less well-preserved areas that were not sampled may have contained the less well-differentiated but mitotically more active parts of the tumor.

An additional problem was not considered. When paraffin blocks are employed as a source of material for flow cytometry, only the nuclei are measured for ploidy. The proportions of nuclei that are from tumor cells, as compared with those that are from normal tissue, are not quantitatively assessed. As tumor cells are usually larger than their normal counterparts (especially well-differentiated squamous components, but others as well), the apparent area of each cell will be large, as will its nucleus. However, when *nuclear* counts of tumor cells are done, their *number* may be quite small compared with normal components. In fact, aneuploid tumor cell nuclei may

See also page 593.

the initial primary tumor but of low frequency. It is a shortcoming of flow cytometry that low-frequency events are missed. Indeed, recent reviews [2, 3] have noted that about 20% of flow cytometric specimens claiming to show diploidy actually contain one or more aneuploid clones when the material is appropriately studied.

The biological likelihood of developing, in the primary neoplasm, additional clones the ploidy of which differs from that initially present was not fully assessed. The contemporary view of carcinogenesis involves sequential mutations; for example, in colorectal carcinogenesis, five or more mutations have been detected [4]. Several oncogene and tumor suppressor gene mutations have been associated with squamous, adenocarcinoma, and small cell carcinoma of the lung; this is doubtless true for the adenosquamous variety also. In many instances, progress through the sequence of tumor evolution—particularly metastasis—is very likely to be accompanied by significant genetic events associated with mutational and chromosomal changes [4]. These changes may be manifested

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represent such a low proportion of the total nuclei extracted from a particular section (especially where there is heavy lymphocytic infiltration) that they may be represented in the flow histogram as an inconsequential fluctuation. If the photomicrographic illustrations in the article by Ichinose and associates are representative of the material used for nuclear extraction and subsequent flow cytometry, normal cell nuclei substantially outnumbered tumor nuclei.

Finally, there is the problem of identifying ploidy levels in cancers of the lung. For estimating ploidy level of nuclei extracted from paraffin-embedded lung cancers, Ichinose and associates used a method that only *assumes* that the dominant left-hand peak represents the G_0G_1 population and is therefore diploid; *no control cells known to be diploid* were introduced into the specimen during the flow analysis. Several ways of correcting this deficit have been reported, but none was adopted for this study. This flaw is likely to be the source of the variation among results in the various reported studies of lung cancer ploidy.

Earlier studies of lung cancer ploidy, done by DNA analysis of individual cells that were each reliably identified as being cancer cells, emphasized the frequency of hyperploidy and aneuploidy [6-8]; other studies, done by flow cytometry, have reported a higher frequency of diploid neoplasms. Some of these differences are surely due to differences in method (statistical or otherwise), but most are likely related to one or more of the various considerations noted above.

In summary, DNA ploidy differences between tumors from different sites cannot be accepted as evidence for lack of relation between the tumors until the following questions are addressed:

1. If the first tumor is a rare event, what is the probability that a second tumor of similar type is related (or unrelated) to the first?

2. Because tumor progression is associated with sequential mutations, and often with chromosomal changes, are DNA ploidy changes expected between a primary cancer and the development of its metastases?
3. Is flow cytometry the best method for assessing DNA ploidy from paraffin-embedded tumor specimens? Should the method be used for assessing rare events?

At this time, we believe that DNA ploidy alone is not an adequately specific marker for distinguishing between two primary lesions or between a primary and a metastatic lesion.

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Evolving Applications of the Maze Procedure for Atrial Fibrillation

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In this issue of *The Annals*, two groups of surgeons present their experiences with performing a surgical procedure designed specifically to ablate atrial fibrillation in conjunction with the repair of other cardiac abnormalities. Bonchek and associates [1] report the application of the maze procedure for paroxysmal (intermittent) atrial fibrillation in a 52-year-old patient who required closure of an atrial septal defect (ASD). They present an eloquent case for the concept of *routinely* adding the maze procedure in patients over the age of 40 years who require ASD closure, their argument being based on the fact that atrial fibrillation and its attendant detrimental sequelae will eventually develop in the majority of such patients. Hioki and associates [2] describe the use of a *modified* maze procedure in conjunction with mitral valve replacement in a 54-year-old patient with mitral stenosis and chronic (continuous) atrial fibrillation.

Although these two excellent reports would appear to share the common theme of promoting the treatment of atrial fibrillation at the same time that other cardiac abnormalities are corrected, the articles actually are quite different in terms of the connotations of the individual cases. Most patients who require closure of an ASD, regardless of age, do not have preoperative atrial fibrillation. In Bonchek's case, the patient apparently did have paroxysmal atrial fibrillation preoperatively and, there-

management strategy would represent the first application of the maze procedure as a prophylactic surgical therapy for atrial fibrillation. Although the maze procedure has proved to be quite promising as a *therapeutic* modality, I am skeptical that our cardiologic colleagues are yet prepared to accept it as a *prophylactic* procedure. This unfortunate but realistic concern, however, does not sway the logic of the recommendations proposed by Bonchek and his associates.

It is extremely important for the reader to understand that the surgical procedure performed by Hioki and associates is *not* the maze procedure. The original description of the maze procedure [3] (Fig 1), as well as the two subsequent modifications that we have made (Figs 2, 3), includes an incision that *completely encircles the orifices of the pulmonary veins*, thereby isolating them from the rest of the heart. Rather than isolating the pulmonary veins with such an encircling incision, Hioki and associates extended the short posterior vertical atriotomy from the mitral valve straight up the posterior wall of the left atrium *between the right and left pulmonary veins* (Fig 4).

We performed this exact procedure on March 8, 1990, in a 50-year-old woman with severe mitral regurgitation and chronic atrial fibrillation. The reason for our placing the single incision *between* the pulmonary veins rather than *around* them was that it had taken us 1 hour of aortic cross-clamp time to repair the mitral valve and, being early in our experience with the maze procedure, we did not feel comfortable in subjecting the patient to the extra cross-clamp time required to perform the encircling incision. As a result, we compromised by placing the incision between the pulmonary veins, a compromise that required substantially less time to perform. The patient had no further atrial fibrillation until approximately 6 months postoperatively when chronic atrial fibrillation again developed, which has continued for the past 2 years.

This unhappy experience taught us two important lessons: (1) any major modification of the incisions used for the maze procedure should be thoroughly tested in the research laboratory before clinical application and (2) the concept upon which the true maze procedure is based is an accurate one. In other words, what better control could one have to demonstrate the efficacy of the maze procedure than an operation almost identical to it that does not work?

Although Hioki's patient has remained free of atrial fibrillation for at least 1 year postoperatively, our experience would indicate that this modification of the maze procedure will not yield results comparable with the true

See also pages 607 and 776.

fore, could be expected to continue to have this arrhythmia postoperatively. Thus, a strong argument can be made for doing something at the time of the ASD closure to preclude the long-term problems associated with postoperative atrial fibrillation in this particular patient. However, the most important connotation of Bonchek's article was that a similar argument could be made for performing the maze procedure in *all* patients over the age of 40 years who require ASD closure even if they do *not* have preoperative atrial fibrillation. This recommendation is based on the available literature, which clearly documents the fact that atrial fibrillation will eventually develop in 50% of patients in this age group who undergo ASD closure. Based on the comprehensive review of the available data by Bonchek and associates, I would concur with their recommendation. However, it is worth noting that such a

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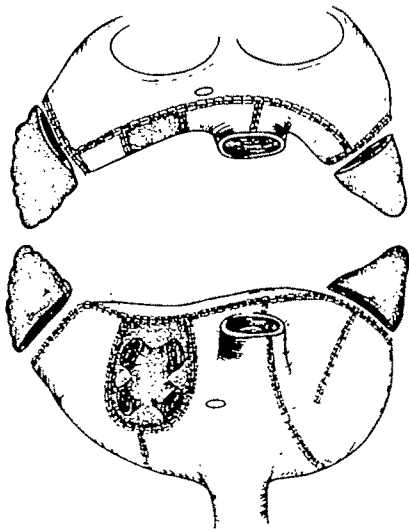


Fig 1. Original maze procedure: This is a schematic depiction of the atria viewed from posteriorly (below) with the corresponding anterior portion of the atria flipped up and depicted above. Note that the orifices of the pulmonary veins are completely encircled and, therefore, are isolated from the rest of the heart.

maze procedure and, therefore, should not be recommended. We believe this modification fails for two reasons: (1) too much contiguous atrial myocardium remains between the right pulmonary veins and the inferior vena cava postoperatively, allowing a macroreentrant circuit to develop around the orifices of these structures (Fig 5) and (2) the orifices of the right upper and right lower pulmonary veins can serve as conduction obstacles around which a smaller macroreentrant circuit can develop (Fig 6).

Despite our concern about the "cardiological correctness" of performing the maze procedure as a prophylactic

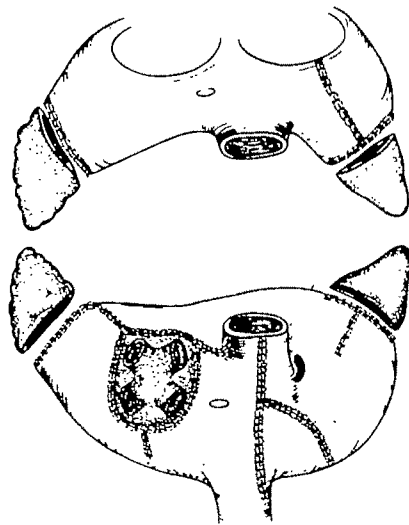


Fig 2. First modification of the maze procedure: Same view as in Figure 1. Again, note that all orifices of the pulmonary veins are isolated from the rest of the heart.

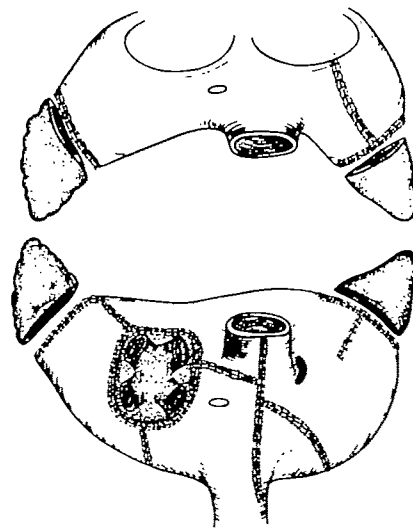


Fig 3. Second modification of the maze procedure: Same view as in Figure 1. Again, note that all orifices of the pulmonary veins are isolated from the rest of the heart.

measure and our belief that the modification of the maze procedure described by Hioki and associates is likely to fail in a substantial number of patients, both of these groups should be commended for expanding the applications of the maze procedure into other areas of cardiac disease in an effort to improve the ultimate outcome of surgical intervention. Such intellectual probing into established clinical practices represents the cornerstone of our specialty, and it is only through such endeavors that our patients may realize the full benefit of the more standard corrective procedures.

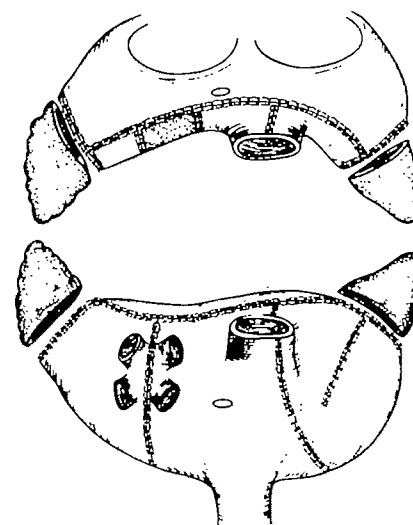


Fig 4. Same view as in Figure 1. These are the incisions described in the article by Hioki and associates [2] and first performed by us in 1990 in an unsuccessful attempt to cure atrial fibrillation in a patient undergoing concomitant mitral valve repair (see text for further discussion). Note that the pulmonary vein orifices are not isolated from the rest of the heart.

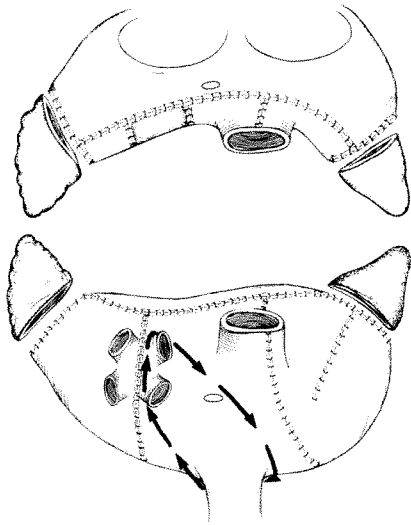


Fig 5. Same view as in Figure 1. Arrows show the potential path of a macroreentrant circuit encompassing the orifices of the right pulmonary veins and the inferior vena cava after the surgical procedure described in the article by Hioki and associates [2].

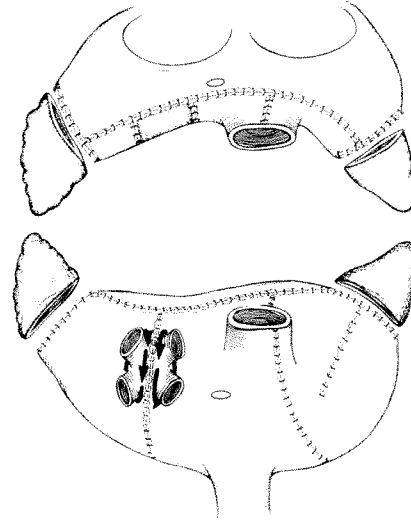


Fig 6. Same view as in Figure 1. Arrows show potential paths of macroreentrant circuits encompassing the orifices of the right and left pulmonary veins after the surgical procedure described in the article by Hioki and associates [2].

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When Does One Replace the Heart in Ischemic Cardiomyopathy?

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Cardiac transplantation is a means of providing near-normal cardiac function in patients with end-stage cardiomyopathy. One-year survival is in the range of 80% to 90%, and 5-year survival is around 65% [1]. The major problem with transplantation is lack of adequate donor supply [2]. On our own service, the yearly attrition on our waiting list for heart transplantation is between 10% and 20%. This is similar to most other transplant centers.

In patients with idiopathic cardiomyopathy, there really is no surgical option other than transplantation. There is an option, however, in patients with ischemic cardiomyopathy. Luciani and colleagues [3] have attempted to analyze how patients will do who have standard coronary revascularization and compare this group with those who undergo heart transplantation or medical therapy. They studied 143 patients with ischemic cardiomyopathy, as defined by left ventricular ejection fractions less than 0.30. The medically treated patients fared the worst, with an actuarial 5-year survival of 28%. The patients undergoing coronary revascularization had a relatively high perioper-

ative angina connotes viable myocardium. We noted that although angina was a predictor of a good result, lack of angina did not predict a poor result. We have attempted to use thallium 201 scintigraphy to predict viable myocardium with mixed results. In our hands, the improvement in ventricular function clearly does not equal that of transplantation. The mean increase in ejection fraction in our patients was 8%. Despite this, the majority attained New York Heart Association class I status.

Coronary revascularization should be the first-line therapy for patients with ischemic cardiomyopathy if there are good distal vessels and a probability of viable myocardium. Clearly, there are just not enough hearts available for transplantation, and the long-term results of revascularization are quite good. If a patient fails revascularization and has persistent heart failure, then transplantation is still an option. A previous coronary bypass graft does not increase the risk of transplantation [5]. There are two clinical questions related to ischemic cardiomyopathy that have not yet been answered. The first question is how to accurately predict that coronary revascularization will be successful. Clearly, the concept of "hibernating myocardium" has to be better diagnosed and defined. The second question is how to predict and prevent late sudden death after coronary artery bypass grafting in this group of patients. Seven of eight late deaths in our series were due to arrhythmias. We are now participating with other centers in the coronary artery bypass grafting-patch (CABG-Patch) trial. This trial consists of randomizing patients who are to undergo coronary artery bypass grafting and have reduced ventricular function to placement of the automatic implantable cardioverter defibrillator. Hopefully, this study will determine if the automatic implantable cardioverter defibrillator does indeed prolong survival after coronary revascularization in patients with ventricular dysfunction.

See also page 719.

ative mortality of 20%, but the actuarial survival for this group at 5 years was 80%. Operative mortality for transplantation was 11.6%, and the actuarial five-year survival was 82% at 5 years. Nineteen patients died waiting for heart transplantation during the study period. Luciani and associates demonstrated that coronary revascularization could certainly be done successfully even in patients with markedly reduced ventricular function. They also noted that medical therapy offered extremely poor results in patients with depressed left ventricular function related to coronary disease.

Although some of the differences in outcome may certainly have been due to patient selection, I agree wholeheartedly with their conclusions. My colleagues and I [4] have previously described 39 patients with preoperative ejection fractions of less than 0.20 who underwent coronary artery bypass grafting. The mean left ventricular ejection fraction in our group of patients was 0.18. There was one operative death (2.6%), and the 3-year survival rate was 83%. Most patients did well, although 3 continued to have severe heart failure; 2 of these 3 underwent successful cardiac transplantation.

There is no doubt that certain patients with severe ischemic ventricular dysfunction will do well with coronary revascularization. The difficulty is in predicting which ones. Luciani and associates suggest that preoper-

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Third-Time Coronary Artery Bypass Grafting: Midterm Results

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Minimal data are available regarding the results of patients who have undergone myocardial revascularization more than twice. The records of 13 consecutive patients who underwent a coronary artery bypass procedure for the third time were reviewed. The indication for operation was unstable angina in all patients. All patients were placed on cardiopulmonary bypass through a median sternotomy. The mean number of bypass grafts placed at the third operation was 1.9 (range, 1 to 3 grafts). A new internal mammary artery graft was placed in 6 patients (2 had prior internal mammary artery grafts). Hospital mortality was 7.7% (1/13). The single death was due to incomplete revascularization in a patient with

poor distal vessels. Three patients required intraaortic balloon pump support postoperatively, and 2 patients had prolonged ventilatory insufficiency. There have been no late deaths. The 12 survivors have been followed up a mean of 44 months (range, 6 to 90 months). Four remain asymptomatic; 5 have mild angina easily controlled with medication. All except 1 are in improved condition compared with their preoperative status. We conclude that a third myocardial revascularization can be performed with low mortality and morbidity and with the expectation of long-lasting symptomatic improvement.

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The efficacy of coronary artery bypass grafting for patients with symptomatic myocardial ischemia is well established in the literature. During the last 10 years multiple reports have documented excellent results after repeat coronary artery revascularization. Reoperative coronary artery bypass operations are increasing in frequency. It is estimated that approximately 18% of coronary artery revascularization cases are reoperative procedures. Lytle and associates [1] documented survival rates of 90% at 5 years and 75% at 10 years after coronary artery reoperation in 1,500 patients. According to Cosgrove and associates [2], as the population at risk for coronary artery disease ages and increases in size the number of reoperative procedures may increase exponentially. Consequently, an ever-increasing pool of patients now is being seen with need of coronary revascularization for the third time.

The Vanderbilt University Medical Center experience with patients who have undergone a third coronary artery bypass procedure has been reviewed to assess patient characteristics, to determine hospital mortality and morbidity, and to evaluate quality of life after operation.

Patients and Methods

The records of all patients who underwent coronary artery bypass grafting at this center during the period April 1, 1985, to April 30, 1992, were reviewed. At Vanderbilt University Hospital and the Nashville Veter-

ans Administration Hospital a total of 2,117 coronary artery bypass procedures were performed. There were 1,830 primary operations (86%) and 287 reoperative procedures (14%). Thirteen patients (0.6%) underwent coronary artery revascularization for the third time. There were 12 men and 1 woman with a mean age of 57 years (range, 46 to 69 years). Their average age at the first operation was 46 years (range, 38 to 57 years), and their average age at the second operation was 51 years (range, 41 to 62 years). The average interval between their first and second operations was 5.7 years, and the average interval between their second and third operations was 5.5 years.

The indication for the third revascularization in all 13 patients was unstable angina that was refractory to medical management. Smoking and hypercholesterolemia were the two most common of the classic risk factors of coronary artery disease present in these patients. Other risk factors included hypertension, hypertriglyceridemia, family history, obesity, and diabetes. All patients underwent preoperative cardiac catheterization to delineate native coronary artery and bypass graft anatomy and to assess left ventricular function. Left ventricular ejection fraction and end-diastolic pressure were measured during catheterization. In some patients left ventricular function was also assessed by surface echocardiography or radionuclide ventriculography.

All operative procedures were performed through a median sternotomy. Cardiopulmonary bypass with mild systemic hypothermia (22° to 28°C) was used with insertion of the arterial perfusion cannula in the ascending aorta in 7 patients and in the femoral artery in 6 patients. The femoral artery and vein were not routinely exposed,

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and the arterial perfusion cannula was inserted in the femoral artery only when a site for cannulation was not available on the ascending aorta. The mean aortic cross-clamp time was 41 minutes (range, 21 to 77 minutes), and the mean pump time was 124 minutes (range, 55 to 233 minutes). Myocardial protection was achieved with antegrade cold (4°C) crystalloid cardioplegia infused through the aortic root. An intraaortic balloon pump was placed intraoperatively in 3 of 13 patients to assist in weaning from cardiopulmonary bypass.

None of these 13 patients had the internal mammary artery (IMA) used as a bypass conduit at their first operation, whereas 2 patients had three IMAs used during their second procedure. At their third revascularization 6 patients had seven IMAs used as bypass conduits. Of the 13 patients, 8 had IMA grafts used during at least one of their three operations.

Revascularization was considered complete only if all major regions of myocardium in the distribution of the right, left anterior descending, and circumflex coronary artery systems were supplied by either: (1) a native coronary artery free of hemodynamically significant narrowing, (2) a previously inserted graft free of hemodynamically significant narrowing, or (3) a new graft inserted at the third operation. Complete revascularization was performed in all but 1 patient, in whom it was impossible to place a graft to the left anterior descending coronary artery secondary to severe diffuse distal disease. Reverse saphenous vein (greater and lesser) and IMA grafts were employed in all patients. The average number of grafts was 2.8 at the first, 2.4 at the second, and 1.9 at the third operation. During the third procedure 10 patients had their left anterior descending system, diagonal system, or both revascularized; 9 had grafts to their circumflex (obtuse marginal) system; and 4 had grafts to their right coronary system.

Results

All patients survived the operation, but there was one hospital death (mortality rate, 1/13 [7.7%]). The death occurred on postoperative day 3 in the single patient who could not be completely revascularized. Autopsy documented the cause of death to be myocardial ischemia and multiple pulmonary emboli.

Eight patients were discharged from the hospital without complication after an average postoperative stay of 8.1 days. One patient sustained a perioperative subendocardial myocardial infarction manifested by ischemic changes on a postoperative electrocardiogram and an elevated level of creatine kinase isoenzyme (MB band > 5%). This patient was discharged without further sequelae on postoperative day 9. One patient was febrile, and blood cultures documented a gram-negative bacteremia. No source of the bacteremia was identified, and after appropriate antibiotic therapy the patient was discharged 12 days after operation. Two patients had a prolonged intensive care unit stay secondary to sepsis and respiratory failure. These 2 patients remained on mechanical ventilatory support for 27 and 46 days, respectively, and 1 required a tracheostomy.

The average preoperative ejection fraction was 0.47 (range, 0.25 to 0.65), and the average left ventricular end-diastolic pressure was 19.5 mm Hg (range, 8 to 26 mm Hg). Those patients discharged without complication had an average ejection fraction of 0.42 (range, 0.25 to 0.65), whereas patients with complications had an average ejection fraction of 0.56 (range, 0.50 to 0.65). The mean left ventricular end-diastolic pressure was 19 mm Hg (range, 8 to 26 mm Hg) in patients without complications and 20 mm Hg (range, 12 to 26 mm Hg) in the patients with complications. If the 2 patients with respiratory failure are excluded the patients were extubated an average of 1.2 days (range, 1 to 2 days) after operation, and they were transferred to a regular floor after an average stay of 3.9 days (range, 2 to 6 days) in an intensive care or step-down unit. The average postoperative hospital stay for all 12 surviving patients was 15.7 days (range, 6 to 57 days). If the 2 patients with respiratory failure are excluded the average postoperative hospital stay was 8.6 days (range, 6 to 12 days).

Three of the thirteen patients (23%) required an intraaortic balloon pump postoperatively. All intraaortic balloon pumps were inserted in the operating room just before weaning from cardiopulmonary bypass. Two patients had the intraaortic balloon pump removed on postoperative day 2, and 1 had it removed on postoperative day 7. Two patients with respiratory failure required inotropic support for 10 and 15 days, respectively. The other patients required no more than 2 days of inotropic support. Three patients remained on a regimen of intravenous antiarrhythmics for longer than 2 days.

No concomitant procedures were performed in these patients. One of the 13 patients required reoperation for bleeding.

There were no wound infections, and no patient experienced a transmural myocardial infarction.

All of the patients have been followed up for a mean of 44 months (range, 6 to 90 months). There have been no late deaths. Four patients have had a documented myocardial infarction at an average of 40.5 months postoperatively. Four patients are free of pain, and 5 have mild exertional angina. One patient has moderate angina at 40 months postoperatively, and 1 has severe angina with congestive heart failure 77 months after operation. One patient had a subxiphoid incisional hernia repaired 11 months postoperatively. There have been no other late complications.

Comment

Reoperative coronary artery bypass procedures are becoming more common, and they constitute nearly one fifth of all coronary artery bypass operations [3]. It is anticipated that the number of multiple reoperative revascularization procedures will continue to increase. Several series have documented overall excellent results in patients undergoing myocardial revascularization for the third time [4-7]. Young age, absence of IMA bypass, incomplete revascularization, New York Heart Association class III or IV, and single-vessel or double-vessel disease were found to be the most important predictors of

repeat coronary artery bypass procedures by Cosgrove and associates [2]. In patients undergoing third-time coronary revascularization, Blakeman and colleagues [5] and Brenowitz and co-workers [4] found that mean age at the first operation was 49.8 and 48.0 years, respectively. These ages are similar to the age at first coronary artery bypass in our group (45.8 years). None of our patients had an IMA graft at their first operation, and most of them experienced unstable angina. Only 4 patients in our group had single-vessel or double-vessel disease at the time of their first bypass procedure.

Lytle and associates [1] demonstrated that left main stenosis, New York Heart Association class III or IV, advanced age, and incomplete revascularization were predictors of in-hospital mortality after redo coronary artery bypass. The single death in this series occurred in a patient who was 46 years of age and had unstable angina and severe left main coronary artery disease. The cause of death was myocardial ischemia due to incomplete revascularization because of severe diffuse distal vessel disease. Brenowitz and co-workers [4] and Cosgrove and associates [2] have reported impaired left ventricular function as a predictor of poor outcome in reoperative coronary revascularization. Five of 13 patients in our series had an ejection fraction of 0.40 or less, and none experienced postoperative morbidity or mortality.

During the period covered by this study 8 patients with profound left ventricular dysfunction were evaluated for persistent angina or congestive heart failure after a second coronary artery bypass procedure. Rather than proceed with an attempt at a third myocardial revascularization these patients all underwent orthotopic cardiac transplantation with no deaths.

Although the risk of a third myocardial revascularization is low, this is not a procedure that is recommended lightly. Patients should have myocardial ischemia with symptoms that are refractory to maximum medical therapy. The minimum acceptable degree of left ventricular function has not been clearly defined, but when there is clear evidence of profound left ventricular dysfunction cardiac transplantation should be considered as an alternative mode of treatment. Inadequate or incomplete revascularization will give rise to suboptimal results, so the patient should have distal vessels that are of reasonable quality and size to allow grafting and significant improvement in myocardial perfusion.

The timing of operation requires considerable judgment. There are no hard data available for critical analysis, but it seems advantageous to operate, whenever possible, only after a maximal effort to stabilize the patient's myocardial ischemia. This may require several days of intensive management with intravenous heparin and nitroglycerin plus aspirin.

As mentioned previously, the femoral vessels are not routinely exposed before the sternotomy incision. An oscillating saw is used in all patients. Minimal dissection is undertaken to expose the ascending aorta and right atrium. Single aortic and atrial cannulation is preferred, but if there is inadequate room on the aorta for arterial cannulation the retrograde femoral approach is em-

ployed. Early heparinization and cannulation are preferred, with most of the dissection of the heart performed once cardiopulmonary bypass has been established. Existing vein grafts are left alone as much as possible. They are neither ligated nor excised.

Internal mammary artery grafts are used whenever feasible, sometimes as free grafts if the anastomotic site on the coronary artery is quite distal. Greater saphenous vein is used as an alternative, as is lesser saphenous vein if there is inadequate length of greater saphenous vein available.

Crystalloid cardioplegia administered antegrade in the aortic root has been employed in the routine fashion. Recently retrograde cardioplegia delivery through the coronary sinus has been used in patients in whom there are obvious or suspected problems with cardioplegia delivery. If there is a patent IMA bypass graft it is carefully protected, and it is clamped with a small soft metal vascular clamp once cardioplegia delivery has been initiated. The aortic cross-clamp usually remains in place until all distal and proximal anastomoses have been performed.

All 12 of the hospital survivors had complete relief of their chest pain early postoperatively and were rendered asymptomatic. The average pain-free interval after their third coronary artery bypass operation was 31 months in the 8 patients in whom recurrent symptoms have developed. Long-term follow-up has demonstrated overall good results with no late deaths. However, one third of the long-term survivors have experienced a late postoperative myocardial infarction.

This series demonstrates that third-time coronary revascularization can be performed with low morbidity and mortality. This group has experienced satisfactory relief of symptoms and no late mortality. Patients who experience symptoms of myocardial ischemia that are refractory to maximal medical management and who have distal vessels amenable to revascularization and reasonably well preserved left ventricular function should be given careful consideration for third-time coronary artery revascularization.

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DISCUSSION

DR HUGH VAN GELDER (St. Petersburg, FL): We recently had a patient in whom we did a third-time redo operation and at the site of the IMA takedown the left ventricle was plastered to the chest wall. Do you do anything to make it easier to come back, either using a membrane or trying to close pericardium to make the operation easier the next time?

DR KEVIN D. ACCOLA (Memphis, TN): I enjoyed your report. I just wanted to make a couple of comments as well as ask you a technical question. We recently reported our reoperative coronary experience from Emory, which was published in *The Annals* in October 1991. In our group we had 53 patients who had either a third or fourth reoperative procedure. Our mortality was the same as yours, 7.5%. Of interest, we also noticed that there was a very short interval between the reoperations in this particular patient population. Between the first and second bypass procedures was 5.26 years, between the second and third was 8.88 years, and between the third and fourth was 4.65 years. Possibly you could expand on these findings as to your thoughts on the cause of the short reoperative period. Do these patients have a more aggressive coronary artery disease process? They did not appear in our review to have any higher incidence of risk factors than usual.

From a technical standpoint, we typically on the second reoperative procedure expose the femoral artery, and on the third and fourth procedure we will usually cannulate the femoral artery and sometimes the vein. How do you decide in which patients you are going to proceed with femoral artery cannulation; is it when you get into a problem during sternotomy or electively?

My final question is in regard to existing vein grafts. We typically at 5 to 7 years will replace a vein graft depending on its clinical appearance either from the preoperative angiogram or at the time of reoperation. What are your criteria for replacement of existing veins and how do you evaluate them, or do you empirically replace these grafts at a predetermined time?

DR LENOX D. BAKER, JR (Norfolk, VA): I was impressed that 85% of your patients were still smoking, and this may answer the question Dr Accola just asked about why the interval is so short. Do you think the situation is similar to that of drug addicts who are still active drug users and come in infected, in whom we do not do second valve replacements? I wonder, considering these results, which are really basically poor long-term results, whether we should consider not doing a third operation until the patient has made some commitment to get off cigarettes and proven it, which is what we also do with our heart transplant recipients. We do not perform transplantation in people who are still smoking. Perhaps we should not do a third coronary artery bypass in a patient who continues to smoke.

DR GEORGE R. DAICOFF (St. Petersburg, FL): I have been listening to these last two reports and I am a little bit confused because we thought that an IMA offered an additional degree of protection and subsequently thought we should do as many arterial grafts as possible. Then we learned that there was a higher incidence of infection when using bilateral IMAs. So then we reverted to uniformly using one IMA and some veins. I am currently experiencing 20% or more redo operations in my

practice; do you now believe we should save the second IMA for the redo? Is there really evidence that two IMAs offer more long-term protection than one IMA and a vein at the initial operation? What are your thoughts about that?

DR MERRILL: I thank all of you for your comments. I will try to answer your questions in order. Certainly adhesions are a major problem in these multiple reoperative procedures. We have not used any of the artificial pericardium or biological forms of pericardium and have for the most part found that it does not seem to make a large difference whether the pericardium is closed or left open. I think the only thing that is really important is to make sure at the time of operation that the bleeding is well controlled and the mediastinum is well drained, and we do make a point of washing the talc off our gloves before every operation in the hope that the absence of talc will lead to less adhesion formation.

Doctor Accola, I am very familiar with your excellent article that was published recently regarding the results at Emory. Clearly, I think these patients do have an aggressive form of coronary artery disease as manifested by their early age at first operation and their fairly rapid requirement for subsequent operations. I really do not have an explanation as to what the factors might be that cause this problem, although clearly the persistence of smoking is a major issue and a major concern. As I mentioned, we do not routinely expose the femoral artery or vein but go ahead and perform the sternotomy and just make a decision at the time of operation as to whether or not there is in fact room on the ascending aorta for arterial cannulation. Also, one has to contemplate the grafts that are already present plus the new proximal anastomoses that will have to be performed. But we will perform femoral cannulation only when there does not seem to be sufficient room on the ascending aorta.

With regard to replacing patent but older vein grafts on the heart, I think that is a matter of considerable judgment. As a general rule, I think the older grafts should be replaced if possible, even if they are patent. We all know that they commonly contain considerably more atherosclerotic disease than is apparent on the arteriogram. The key factor to consider is what you are going to replace the conduit with. Does the patient have sufficient remaining good-quality artery or vein that will be better conduit than what is already present? Again, I think that calls for considerable individualized judgment.

With regard to Dr Baker's comment, I really do not know how tough we should be on these people who are persistent smokers. Certainly that is one of the risk factors that could be modified, but a fair number of them are overweight, they do not really follow regular exercise regimens, and they do not follow proper low-cholesterol, low-fat diets. So there are many aspects to their illness that need to be addressed, and we will all need to be thinking about these factors in the future.

With regard to the last point, I must admit I am really not sure exactly what the proper philosophy of IMA use should be. We are learning more and more that multiple IMA bypass grafts and extended IMA bypass grafts may in fact be good, they may prolong survival, and perhaps we should be using the IMAs more extensively in the hope of preventing reoperation, but I think it will be a long time before we have the definitive answer.

Penetrating Injuries of the Aortic Arch and Its Branches

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Acute cardiac failure, pulmonary edema, and ischemia of the brain, cord, and other structures pose special problems with trauma to the aortic arch and its branches. Data on 93 such cases are reported. Diagnosis was made by clinical examination in hemodynamically unstable patients and led to immediate operation in 61.3%. Patients in stable condition had angiography, which localized the injury and allowed planning of incision and bypass shunts. In left subclavian artery injuries, anterior thoracotomy was best for proximal control regardless of wound entry sites; midline sternotomy with sternocleidomastoid extension was usually adequate for other

vessels. Flow was reestablished in all carotid injuries; there were no neurological complications. Temporary or permanent bypass shunts during periods of proximal aortic occlusion were valuable in decreasing cardiac afterload, maintaining circulation to the brain, and allowing an unhurried methodical approach to the hematoma. Occlusion of one or more venae cavae alleviated acute cardiac dilatation during brief periods of ascending aortic clamping. Associated trauma contributed to the high mortality.

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Pulmonary edema, acute heart failure, and irreversible ischemia of the brain, spinal cord, kidneys, and viscera are special problems associated with control of exsanguinating hemorrhage from penetrating trauma to the aortic arch and its branches. Many injuries localized to the anterior surface of the arch or its branches (more than a centimeter distal to their origin) can be easily repaired by simple digital pressure or partial occlusion and suture, whereas more complex injuries involving the posterior surface of the arch or the origin of innominate or carotid arteries may require bypass techniques to avoid these potentially fatal complications. Surgical approaches should be directed at decreasing cardiac afterload and maintaining oxygenated blood flow to the brain and distal body.

For these purposes, Symbas and Sehdeva [1], in 1970, reported the use of a temporary shunt from the ascending aorta to the innominate artery for repair of a stab wound of the arch. This concept was extended in 1973 by DeMeester and associates [2], who used a heparinized shunt from the ascending aorta to the femoral artery to maintain distal circulation and decompress the heart during repair of an arch injury. Rather than temporary shunts, the Houston group [3], in 1982, introduced the use of a permanent prosthetic bypass graft from the ascending aorta to the distal carotid or innominate artery before repair of the arch and innominate artery. In 1984, we adopted the routine use of both temporary and permanent bypass shunts for managing these injuries and expanded the use

to Y grafts to both carotid arteries before disturbing the hematoma or attempting repair.

These injuries are uncommon [4, 5]; Rich and associates' report [6] of 1,000 arterial injuries from the Vietnam war includes only three innominate and eight subclavian artery injuries. The development of well-organized trauma systems is leading to increasing numbers of such victims of urban warfare reaching the treatment facility alive.

To summarize our experience and arrive at reasonable recommendations, we are reporting our more recent experience of penetrating injuries to the aortic arch (from superior pericardial reflection to the aortic isthmus) and its branches—innominate, common carotid, and subclavian arteries—that we treated at their initial trauma episode during the 8 years ending September 1, 1992. Only carotid artery injuries that resulted from thoracic wounds or wounds of the base of the neck or supraclavicular spaces that passed into the thorax are included.

Material and Methods

We reviewed the medical records of 93 consecutive patients who sustained penetrating injury (63.5% of which were gunshot wounds) of the aortic arch and its branches and were admitted to the Elvis Presley Trauma Center, Memphis (Table 1). Most patients (79.7%) were male; they had a median age of 26 years. Among the factors studied were age, mechanism of injury, hemodynamics, preoperative and postoperative neurological findings, associated trauma, diagnostic methods, anatomy of vascular injury, surgical exposure, use of shunts, and mortality. When there was evidence of massive or pulsatile bleeding or persistent hemodynamic instability, the patient was im-

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Table 1. Clinical Outcomes of Entire Series

Site	Number	Not Resuscitated	Operated Patients		Total Survivors
			Lived	Died	
Aorta	27	9 (33.3%)	11 (61.1%)	7 (38.9%)	11* (40.7%)
Innominate	6	...	5 (83.3%)	1 (16.7%)	5 (83.3%)
Carotid	31	3 (9.7%)	25 (89.3%)	3 (10.7%)	25 (80.6%)
Subclavian	29	...	25 (86.2%)	4 (13.8%)	25 (86.2%)
Total	93 (100.0%)	12 (12.9%)	66 (81.5%)	15 (18.5%)	66 (71.0%)

* Four deaths resulted from other injuries. Excluding these, survival related to the aortic arch injury alone for operated patients would have been 83.3%.

mediately operated on without further study. All patients in stable condition demonstrating pulse deficit, major hematoma, widened mediastinum, or missile tracts thought to be near major arteries had aortograms for precise anatomical diagnosis and to plan surgical exposure and the possible use of shunts ("selective" operation). Operating rooms and an arteriographic suite are integral to the Trauma Center, thus avoiding unnecessary and dangerous transportation of these patients in critical condition.

Operative Technique

The two basic incisions usually used were (1) midline sternotomy, with cervical extensions over one or both carotids when needed, and (2) an anterior left thoracotomy through the fourth intercostal space (with dislocation of cartilage) for exposure of the left subclavian artery. The latter incision was extended by partial median sternotomy, neck incision, and excision of half the clavicle, as required. Entrance wounds in the left supraclavicular fossa and associated with a left pneumothorax or hemothorax were assumed to be subclavian artery injuries for purposes of selecting the incision. When an arteriogram was available, the plan of the operation was based on the site of vascular injury. In the group having immediate operation, the operative approach was chosen based on suspected injury and the exact technique was modified as necessary after the chest was open.

Injuries on the anterior surface of the arch or branches further than 1 cm away from the aorta were usually managed by digital pressure or tangential partial occlusion clamps and suture. Intermittent aortic occlusion, either partial or complete, and caval occlusion were useful adjuncts both for exposure and for decreasing blood pressure while suturing. For larger wounds and gunshot injuries, large felt pledgets or patches of prosthetic material were used. With involvement of the superior surface of the arch and origins of the innominate or carotid arteries, more complex procedures were usually considered necessary.

When exposure of the concavity and posterior surface of the aorta was necessary, the pulmonary artery and aorta were separated by sharp incision, followed by division of the pericardial and fascial tissue from *within* the pericardium (Fig 1). Dissection of the concave and posterior surfaces of the arch from *outside* the pericardium is hazardous, as the fibrous layer of the pericardium

blends into and forms the aortic adventitia. Dissection from without leads to an apparent cleavage plane, which may actually be within the aortic wall [7].

Principles aimed at avoiding irreversible ischemic damage to vital organs or distension of the left ventricle were followed (Table 2). When practical, blood flow to the distal arterial bed was always reestablished. When a *midline* incision was used, the pericardium was immediately opened vertically, before the hematoma was entered. This allowed tapes to be easily placed around the cava(e) for cardiac inflow occlusion and around the ascending aorta for temporary partial occlusion while the repair was effected. While bleeding was controlled by the hematoma or by digital pressure, distal control of the carotid artery (or arteries) was obtained. When compromise of carotid flow was anticipated, shunts were established *before* disturbing the hematoma or bleeding site (Fig 2). This allowed both decompression of the aorta and left heart and flow to the brain during vascular repair. The proximal end of a graft or shunt was placed into the intrapericardial aorta and the other end was placed in the carotid artery distally, before the hematoma was entered. When grafts were used, they were left in situ as bypass grafts; temporary shunts were removed when the repair

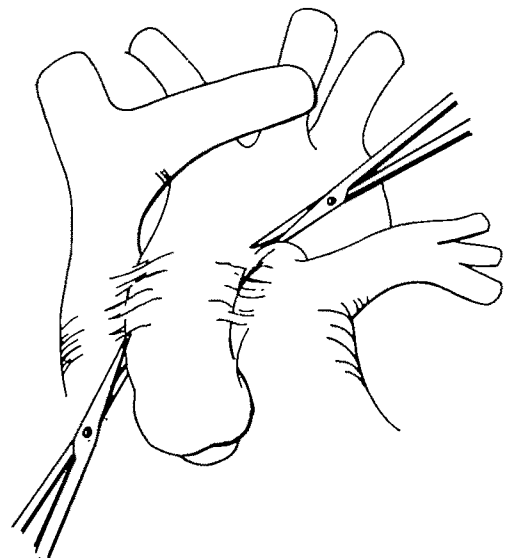


Fig 1. Exposure of the concavity and posterior surface of the aortic arch begins with dissection from within the pericardium (see text).

was completed. Although available in the Trauma Center, cardiopulmonary bypass was used in only 1 patient (patient 3).

When the injury involved the origin of the innominate or carotid artery, the bypass prosthetic graft was left in place permanently and the end of the carotid was oversewn. When the injury did not involve the origin of the branch vessel or continued hemorrhage was a problem, a temporary shunt (see Fig 2) with primary repair or interpositional prosthesis became the preferred technique; this was faster and led to use of less prosthetic material in the narrow confines of the thoracic inlet. The intrathoracic carotid was never ligated without bypass grafting. Primary repair was done when feasible [8].

Illustrative Cases

Both the applications of these principles and some difficulties in their use are illustrated by the following three case reports.

PATIENT 1. A man sustained a stab wound in the right supraclavicular space. Initial pulsatile bleeding was controlled by pressure. Aortogram revealed injury to the aortic arch at the base of the innominate and left carotid arteries. There was associated filling of the left innominate vein and superior vena cava. Repair involved bypass Y shunts to both common carotid arteries followed by brief, intermittent periods of aortic cross-clamping and partial caval occlusion, while the aorta was repaired with pledgeted sutures (see Fig 2). The innominate veins were repaired by simple suture. There were no major complications.

PATIENT 2. This man had a gunshot wound to the left chest. Emergency anterolateral thoracotomy for massive bleeding revealed through-and-through wounds of the aortic arch. The anterior aortic wound and lung were repaired, while the posterior aortic wound was tampon-

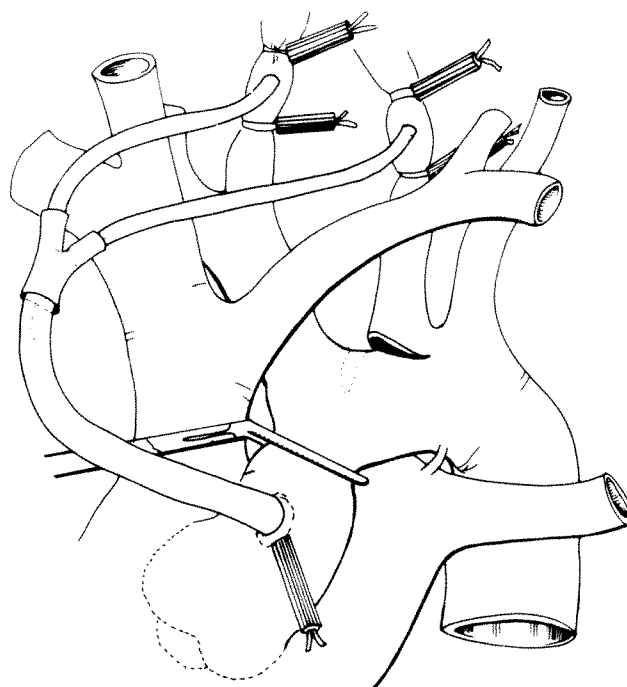


Fig 2. (Patient 1.) Bypass shunt from ascending aorta to carotid arteries is established before attempting suture of the arch. An injury to the posterior surface of the junction of the brachiocephalic veins and the caval tapes are not shown.

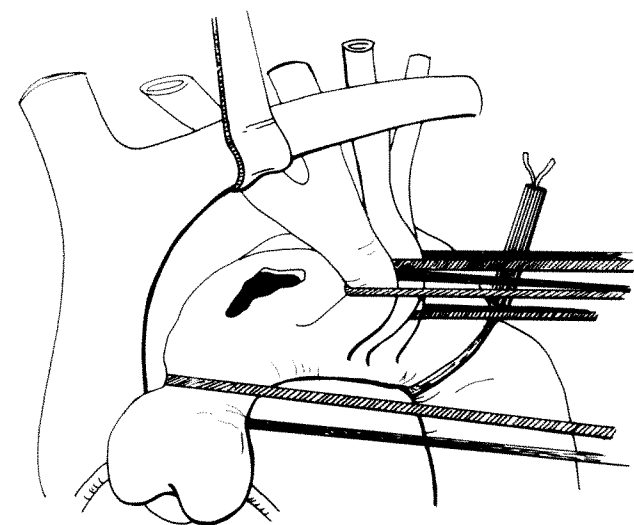
aded. A midline incision was necessary for adequate exposure of the posterior aortic wound. The pericardium between the aorta and pulmonary arteries was divided, followed by division of the posterior fascial attachments of the aorta. Exposure and repair of the posterior defect was done in intermittent steps by temporary tape occlusions of aortic branches, intrapericardial control of the aorta, and periods of venous inflow occlusion (Fig 3). Although the patient later died of complications of prolonged shock, this case is useful in emphasizing the necessity for exposure of the posterior arch from the midline. Had the location of the posterior wound been known before the necessary emergency thoracotomy, use of partial cardiopulmonary bypass may have been of benefit.

PATIENT 3. This man sustained a stab wound in the right supraclavicular space with a hunting knife; an aortogram demonstrated a large aorto-left innominate vein fistula. The groin vessels were exposed as a midline thoracotomy was begun. Massive bleeding was encountered upon opening the supramanubrial fascial space; cannulation was performed and partial cardiopulmonary bypass was begun before the sternum was divided. Pressure controlled the hemorrhage while the pericardium was opened and the incision extended along the left carotid sheath. Ascending aorta, superior vena cava, and neck vessels were controlled with tapes. The left innominate vein was almost severed; it was divided, allowing visualization of the anterior and superior surfaces of an extensive aortic laceration (Fig 4). Full cardiopulmonary bypass through the right atrium was instituted with systemic

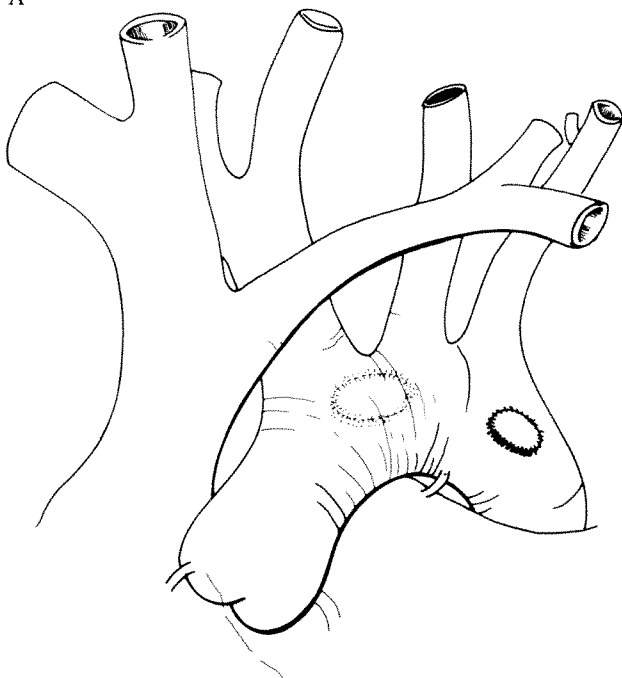
Table 2. Surgical Principles Used In Repair of Aortic Arch Injuries

Principle	Application
Local control	Pressure only
Proximal control	Intrapericardial
Distal control	Tapes: aorta, carotid(s), & innominate
Maintain flow ^a	Bypass shunts:
From ventricle (1 min)	ascending aorta to
To brain (5 min)	carotid(s)
To cord, viscera (30 min)	
Prevent hypertension of left ventricle, pulmonary veins, central veins, cerebrospinal fluid	Arterial shunts and caval occlusion
Exposure of injury site	After proximal and distal control
Reestablish distal circulation	Repair or graft

^a Time of occlusion of arterial flow was kept below indicated times whenever feasible. Hypothermia allows some safe prolongation.



A



B

Fig 3. (Patient 2.) (A) Exposure of gunshot wound on the posterior surface of arch, after dissection from within the pericardium and control of all branches. Caval tapes for inflow occlusion and distal aortic wound are not illustrated for clarity. (B) Completed repair using prosthetic patches.

hypothermia and with cold cardioplegia. The ascending and descending aorta were cross-clamped (at 25°C), and the aorta was dissected and repaired with pledgeted sutures. Aortic cross-clamp time was 19 minutes, followed by 15 minutes of unclamping and then another 22 minutes of reclamping. The patient made an uneventful recovery.

Although this patient could have been handled as patient 2, cardiopulmonary bypass allowed a more controlled situation. Both patients could have benefited from

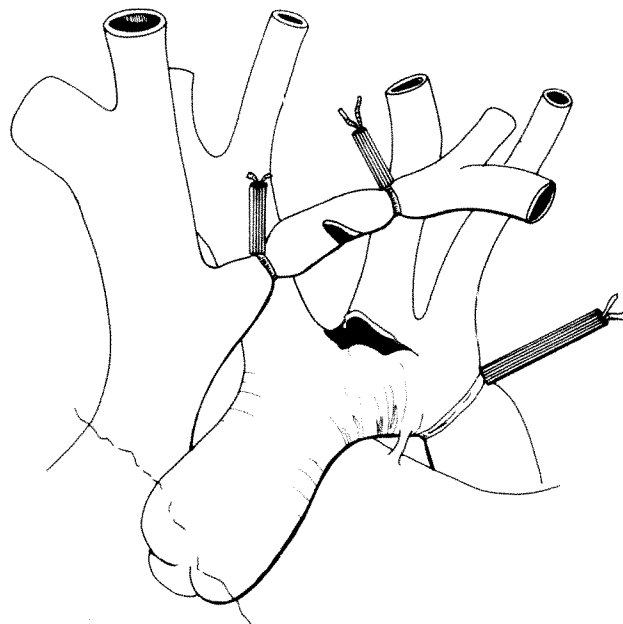


Fig 4. (Patient 3.) Large laceration of left innominate vein and aorta, with functioning arteriovenous fistula. Repaired with hypothermic cardiopulmonary bypass.

temporary bypass shunts from the ascending aorta to the distal carotid arteries, but shunts were not used in either because of the inability to control hemorrhage without occlusion of the ascending aorta after the chest was opened.

Repair of all major vein injuries has been our policy since 1964; however, this has not always been feasible without an intervening graft, which we did not use in the acute trauma setting. No caval ligation was done, although several cavae and innominate veins were sutured without problems.

Results

Associated injury was present in most patients (Table 3) and accounted for several of the deaths.

Fifty-seven patients (61.3%) were hemodynamically unstable; 12 of them (12.9%) died during attempted resuscitation before definitive operation (see Table 1). All had

Table 3. Associated Injuries to Other Structures

Injury to	Number	Percent
Major vein	21	22.6
Trachea	8	8.6
Esophagus	7	7.5
Lung	7	7.5
Spinal cord	6	6.5
Bracheal plexus	5	5.4
Heart	4	4.3
Abdomen	4	4.3
Total (includes other injuries)	77	82.8

injury of the aortic arch, proximal carotid artery, or both. The other 45 unstable patients were immediately operated on without angiograms.

In the 36 patients in stable condition operation was delayed until angiography was performed. Arteriovenous fistulas were demonstrated in 4 of these. In 4 patients not having angiograms, the incision was suboptimal and sternotomy became necessary. Three of these had emergency anterolateral thoracotomies for relief of cardiac tamponade. Another patient with massive left hemothorax was explored through a left posterolateral thoracotomy, but exposure of the posterior arch was not possible and a midline thoracotomy became necessary (patient 2).

All *aortic* injuries were repaired, usually with direct suture over felt pledgets, but on several occasions with prosthetic patches to avoid undue tension on the sutures. Digital pressure or partial occlusion clamps were usually adequate for control during repair. Of 18 patients who underwent operation, cardiopulmonary bypass was used in 1, aorto-carotid shunts in 3, and aorto-innominate shunts in 3. No such adjuncts were used in the other 11 patients, whose injuries were repaired without significant periods of carotid occlusion. Of the 18 patients who reached the operating room alive, 11 survived. Four patients died of other trauma: 1, of an extensive gunshot wound to the heart; 2, of abdominal injuries; and 1, of tracheal injury and asphyxia (see Table 1). Considering only the aortic injury (ie, hemorrhage, operating room deaths, cardiac malfunction, and neurologic complications), the injury-specific survival rate after surgical repair of aortic arch injuries themselves was 83.3%.

All *innominate artery* injuries were repaired or bypassed; only 1 patient died, unrelated to hemorrhage or complications of the innominate artery injury. None had neurologic defects. Bypass shunts were used in 4 patients who had shunts from the ascending aorta, and 1 had a bypass shunt from carotid artery to carotid artery before the chest was entered.

Three of the 31 patients with *common carotid artery* injury were agonal on arrival and definitive therapy was not possible before death. Two of the 28 patients operated on had obvious hemiplegia on admission; there was no improvement after operation. Twenty-six of the 28 patients survived to have carotid artery repairs. Bypass shunts, four permanent and one temporary, were used in these patients. No new or worsening neurologic symptoms developed in any patient after repair or grafting of the carotid artery. Two patients, both in profound shock, died on the operating table of associated injuries and could not be neurologically evaluated.

Of patients with *subclavian artery* injuries, half had primary repair; in 1 the subclavian artery was ligated and in the others it was repaired using grafts. Distal arterial flow was good in all patients. Two patients who had major venous trauma had residual edema of the arm after ligation of subclavian veins; this slowly improved over many months. Concomitant brachial plexus injuries were crippling in 3. The only amputation was of a single finger.

Comment

This retrospective, uncontrolled analysis of a group of patients with a broad spectrum of major injuries and of varying clinical status precludes meaningful statistical analysis. Although the general policies of Table 2 were in use during this series, they could not always be followed. Even with 27 years' experience with similar injuries [9] before this series, details of surgical management still changed during this period. Simplification of incisions and more use of bypass shunts were the major evolutionary changes during these 8 years.

Pulse deficits were of little diagnostic help in these patients; they were noted in only a few patients with firearm injuries of the subclavian artery. Hematomas of the base of the neck or gross arterial bleeding were of no aid in identifying the site of vascular injury. Unilateral hemothorax was usually of help in delineating the injury. The major indication for aortogram was known or suspected wound entry into the mediastinum or base of the neck. When the patient was in stable condition, aortograms were of great help, not only in diagnosis, but especially in planning the operation. In the selective group, we routinely did esophagograms only in those whose entry wound was in the base of the neck. Most of these patients were too uncooperative, either from trauma, drugs, or alcohol, to safely have an esophagogram. Of the seven esophageal injuries, six were repaired at initial operation and one was not diagnosed until serious postoperative infection occurred.

About a fourth of all patients had simultaneous major venous injuries, and an arteriovenous fistula was demonstrated in 4 of the 36 patients (11.1%) who had arteriograms. If the same incidence were true in those patients who did not have an arteriogram, one could expect as many as nine or ten fistulas. A significant correlation of arch injuries and arteriovenous fistulas has also been noted by others [7].

Large vein-ways in the legs, an arterial catheter in the right radial artery, and the use of autotransfusion devices are important basics in the management of these patients.

In previous years we frequently used a Sauerbruch incision for exposure of the innominate and subclavian arteries; its use has steadily diminished. A midline sternotomy with sternocleidomastoid extensions was usually adequate for the innominate artery; a posterolateral thoracotomy served for most of the left subclavian artery injuries resulting from thoracic wounds. However, wounds of the base of the neck involving the left subclavian arteries and extending into the thorax are usually best managed by anterior thoracotomy for proximal control of the artery, a supraclavicular incision with division of the sternocleidomastoid muscle, and clavicular resection as needed for distal control and repair. A full Sauerbruch incision may be necessary if still further exposure is needed.

The issue of ligation versus reconstruction of the carotid artery has received much attention in the literature. In 1974, it was demonstrated [10] that repair of the intrathoracic carotid artery could be associated with massive

cerebral infarction. By 1991, it had become obvious that about half of the deaths after innominate and carotid injuries were due to cerebral infarction caused by *ischemic*, not reperfusion, infarction [11]. Our experience leads us to recommend bypass shunts from the intrapericardial aorta to one or both carotid arteries before exposing the bleeding site when injury to innominate or intrathoracic carotid artery is known or strongly suspected. Only about 20% of patients have a "normal" circle of Willis; preoperative and intraoperative shock and hypoxia contribute to cerebral ischemia, and there is high probability of prolonged occlusion of the carotid artery during dissection and vascular repair. Fabian and associates' [8] recent extensive review of the literature and their experience with a large series of carotid injuries led to conclusions that (1) there is no valid reason to avoid carotid artery reconstruction, (2) there are some patients in whom other impairments (eg, alcohol, drugs, shock) prevent proper preoperative neurological evaluation, (3) there are some patients with neurologic defects whose condition may actually improve after revascularization, and (4) patients with preoperative neurologic defects are seldom, if ever, harmed by reconstruction. None of the patients in this series had worsening neurologic status after flow was reestablished. The fear of "hemorrhagic infarct" of the brain after reestablishing carotid artery flow seems misfounded.

A careful study of the use of shunts has not been possible because of the rarity of these injuries. A recent report [12] of 30 years' experience with the use of shunts in 31 patients with penetrating (24) and blunt (7) injuries of the innominate artery, however, leaves little doubt that this should now be the accepted method of management.

There is a widespread aversion to the use of systemic heparinization in the severely injured patient. In this series of penetrating trauma, we used systemic heparin in doses of about 100 to 150 U/kg, while temporary shunts were in use or when a patient's carotid artery was occluded. We have used full systemic heparinization (300 U/kg initial dose) in more than 100 cases of blunt injury of the thoracic aorta or carotid artery. Most of these patients had concomitant injuries, including head, liver, or spleen disruptions. We have been unable, in spite of prospective critical observation, to demonstrate clear deleterious effects of short-term heparinization, except in patients with severe pulmonary contusions. Others have reported similar experiences [13].

During brief periods of aortic occlusion, the left ventricular afterload abruptly rises. Ventricular dilatation and resultant damage to the myocardium is a real threat. Continuous observation of the electrocardiogram and heart is necessary during these periods. Bradycardia usually occurs as the heart dilates. When a heartbeat drops to 50/min or electrocardiographic signs of ischemia evolve, the occlusion should be released as quickly as possible. In our clinical experience, and in the literature, the deleterious effects on the heart seem to be ameliorated by simultaneous caval occlusion. We have confirmed this in the animal laboratory (Van Voorst and Pate; unpublished results). Theoretically, the beneficial effects of caval occlu-

sion should extend to the lungs and cerebrospinal fluid pressure. Hypovolemia, as suggested by the work of Martin and associates [14], is probably beneficial until repair is complete.

Elevated central venous pressure results in elevated cerebrospinal fluid pressure with consequent decrease in blood flow to the central nervous system. With aortic occlusion resulting in such an increase in cerebrospinal fluid pressure, superimposed on decreased carotid blood flow during clamping, cerebral ischemia is increased on the clamped side and unilateral cerebral edema on the unclamped side might be expected. Hypovolemia, again, might help prevent this effect.

Essentially all of these patients remained on mechanical ventilation for more than 24 hours and most showed varying evidence of pulmonary dysfunction. Shock and massive intravenous fluids are major factors in the disturbed physiology, but the rise in pulmonary venous pressure with partial aortic occlusion certainly might contribute. Again, brief periods of caval occlusion or hypovolemia should be of value in alleviating pulmonary damage. Robicsek and Matos-Cruz [15] recently used electrically induced ventricular fibrillation for these purposes.

Postoperative paraplegia, which occurs in up to 35% of cases of occlusion at the distal arch required for repair of traumatic rupture of the aorta, was not recognized in these patients with penetrating wounds. This is probably due to the fact that periods of proximal aortic occlusion long enough to produce cord damage resulted in fatal cardiac dilatation or cerebral ischemia.

Although patient 3 had a favorable outcome after the use of cardiopulmonary bypass, we believe that most patients (91/93) were more expeditiously managed by the use of arterial bypass shunts and brief caval and aortic occlusion. Retrospectively, in only 2 patients, both with large through-and-through gunshot wounds of the arch, do we believe that cardiopulmonary bypass would have been of value. In both patients necessity for prompt control of the hemorrhage precluded use of cardiopulmonary bypass, even though only 30 to 45 minutes are needed for its set-up.

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DISCUSSION

DR HOOSHANG BOLOOKI (Miami, FL): I enjoyed this presentation very much and had the privilege of reading the manuscript earlier. I would like to congratulate Dr Pate and associates for doing admirable work on these very ill patients. This series of 93 patients actually is one of the largest reported series in the world literature. We have had an experience similar to this but not in as many patients. We have our experience summarized in a chapter in a book titled *Trauma Management* edited by the late Dr Kreis [1]. We entirely agree with your recommendations in managing this injury.

The points that you bring up, and I think they should be reemphasized, are mainly three. First, control the bleeding as fast as you can; second, establish blood flow distally if at all possible and do not just tie off the artery; third, during hypotension periods either incidentally (or because of clamping the vena cava, as you have suggested, and it is a very good idea) continue to work aiming at control of bleeding specifically around the aorta itself and the aortic arch. In other words, use the hypotensive periods to the patient's advantage by controlling the major branches of the arch.

I think it is important to note, as you are indicating, that the farther away the injury is from the arch the greater is the need for a shunt or some kind of bypass. Conversely, for injuries on the aortic arch, especially around the arch or behind the arch, heart-lung bypass is needed. There is no doubt that a heart-lung machine is used in a small number of these patients. It is used more often when angiography delineates the lesion and the operation is planned. In fact, we have lost some patients due to central or arch injuries because we did not have an angiogram. Such a study cannot be done in a patient who is bleeding out, as you indicated already, and as a result one does not know the extent or location of the injury. I think it is important to do a very good physical examination, especially if the injury is a day or two old. A systolic murmur is an important finding because that would allow for better patient management and work-up. The murmur may point to the presence of an arteriovenous fistula. An angiogram, whenever possible, is an invaluable guide to location of injury and hence the method of management.

I have three questions. First, what would you do with an enlarging mediastinal hematoma if the patient is in stable condition and the aorta is intact? Would you explore it or leave it alone and treat the patient conservatively? Second, if there is an acute brain injury (or mild stroke) due to a carotid lesion (cut-off by a flap or by external pressure but without acute carotid bleeding)

would you reestablish the blood flow to the distal carotid artery, or if the neurologic dysfunction is not serious would you wait and intervene at a later time, say a few weeks? Third, around the aortic arch there are many nerves, especially the phrenic, vagus, and recurrent laryngeal. I have had at times problems with these patients after I have done a successful operation on the arch in that they have been respirator dependent. Have you had any problems with that, and what special maneuvers do you use to identify these nerves in the bulk of the hematoma? I thank you again for a fine presentation and congratulate you for good work.

DR PATE: I appreciate your comments, Dr Bolooki. First, a mediastinal hematoma in a patient in stable condition is a definite indication for aortography; most of the time, a major vascular injury will be seen. When an aortogram cannot be obtained, consideration must be given to surgical exposure.

In relation to aortic injuries, we cannot answer the question about completed strokes because, even though this is a very large series, we had too few strokes. There is a lot of information in the literature in relation to neck injuries. As far back as 1974, it was known that revascularization of the carotid artery could result in hemorrhagic infarction. By 1991, it was obvious that about half of the deaths after carotid trauma were due to cerebral infarction, usually *ischemic*. The fear of reperfusion infarction after carotid injury repair is probably based on a myth. An occasional patient will show some improvement after reconstruction. Confusing the issue is the fact that many of these patients are in shock or under the influence of alcohol or drugs and cannot be evaluated preoperatively. Yes, circulation should always be reestablished regardless of neurological findings.

Most of the time, the phrenic nerve can be identified by feel as the hematoma displaces it medially and anteriorly. The reasons for the difficulty in getting a patient off the ventilator place us in the area of opinion rather than facts—I could preach a sermon. Most of these patients are “drowned” during the resuscitation process with 18 to 20 L of crystalloid. They have many reasons for difficulty in weaning. I do not believe this is unique to phrenic or recurrent nerve injury.

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DNA Ploidy Pattern of Each Carcinomatous Component in Adenosquamous Lung Carcinoma

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The relationship between adenocarcinomatous and squamous carcinomatous components in 12 surgically resected adenosquamous lung carcinomas was analyzed using DNA flow cytometry. Well-preserved parts of the tumor showing either adenocarcinoma or squamous cell carcinoma were identified on paraffin blocks. The cells obtained from each component were stained with propidium iodide for DNA flow cytometry. In the analysis of DNA flow cytometry, both components in the same tumor were defined as being related to each other when

they showed diploidy or when at least one DNA index of abnormal clones between two aneuploid components was identical. According to these criteria, 8 (67%) of the 12 tumors showed a relationship between adenocarcinomatous and squamous carcinomatous components. This suggests that, despite the different phenotypes, both components of some adenosquamous lung carcinomas may share similar biological characteristics.

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Adenosquamous lung carcinoma is rarely seen compared with other histologies such as squamous cell carcinoma, small cell carcinoma, large cell carcinoma, and adenocarcinoma of the lung. The incidence reported in surgical resection series [1, 2] is only approximately 2%. Thus, the biological behavior and clinical characteristics of adenosquamous lung carcinomas have not been well described.

Recent studies indicate that all lung cancers, including mixed cell types, arise from a common stem cell [1]. Therefore, one of the most interesting questions about the biological behavior of adenosquamous lung carcinoma is whether the adenocarcinomatous and squamous carcinomatous components in the same tumor share some similar biological characteristics. In the present study, we used DNA flow cytometry to examine this issue.

For editorial comment, see page 576.

Material and Methods

The lung tumors of 19 patients who underwent pulmonary resection at National Kyushu Cancer Center from June 1979 to May 1990 were diagnosed as adenosquamous lung carcinoma. According to the pathological criteria of the Japan Lung Cancer Society [3], tumors identified as adenosquamous carcinoma of the lung should show well-defined squamous components (ie, intracellular keratin or intercellular bridges) and adeno components (ie, glandular, tubular, or papillary structure) on routine microscopic

examination using hematoxylin and eosin staining. In addition, each component should occupy at least 20% of the tumor area obtained by cutting the tumor so as to expose the largest tumor surface. Although the 19 resected tumors fulfilled these criteria, 6 tumors were excluded before DNA flow cytometric analysis because of a lack of suitable specimens. Pathological staging was done according to the new international staging system [4]. Survival after operation was recorded as of September 1991.

Flow cytometric analysis of cellular DNA content was performed using paraffin-embedded blocks of 13 surgically resected tumors. Well-preserved areas of the tumor showing either adenocarcinoma or squamous cell carcinoma were chosen on slides, and the corresponding areas on the paraffin blocks were identified. A single cell suspension was made, and the cells were stained with propidium iodide according to the method described by Tosi [5], Vindeløv [6], and their associates. The stained cells were analyzed on a fluorescence-activated cell sorter-CAN analyzer (Becton Dickinson, Mountain View, CA). At least 20,000 cells from each specimen were examined, and the DNA content per cell, measured by fluorescence intensity, was recorded and displayed in a histogram. The resulting DNA histograms were interpreted without knowledge of patient data.

The DNA index was calculated as the ratio of the aneuploid G_0G_1 peak to the diploid G_0G_1 peak. When only one G_0G_1 peak (DNA index = 1) was observed, the tumor was considered to be diploid. Tumors that had evidence of at least one distant G_0G_1 population (DNA index > 1.0) in addition to a diploid stemline were classified as aneuploid. The lowest peak was assumed to represent the diploid G_0G_1 peak (DNA index = 1). Samples in which the coefficient of variation of the diploid

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Table 1. Summary of Data on Tumors With Similar DNA Ploidy Pattern

Patient No.	Pathological TNM Stage	Diploid Component or DNA Index in Aneuploid Component		Survival After Operation (mo)
		Adenocarcinoma	Squamous Cell Carcinoma	
1	T1 N0 M0	WD (20) ^a Diploid	MD (80) Diploid	Alive, 124
2	T1 N0 M0	MD (50) 1.767 ^b	MD (50) 1.733 ^b	Died without recurrence, 47
3	T2 N0 M0	MD (60) Diploid	MD (40) Diploid	Died, 26
4	T2 N0 M0	PD (60) 1.151, 1.566, 2.094 ^b	MD (40) 1.693, 2.080 ^b	Died, 10
5	T2 N2 M0	MD (20) Diploid	PD (80) Diploid	Alive with recurrence, 50
6	T2 N2 M0	MD (40) Diploid	MD (60) Diploid	Alive, 16
7	T2 N2 M0	MD (20) 1.983 ^b	MD (80) 1.862, 2.069 ^b	Alive with recurrence, 14
8	T2 N0 M1	WD (30) 1.949 ^b	MD (70) 1.950 ^b	Died, 3

^a Numbers in parentheses are percentages of largest cut surface area of tumor occupied by component.

^b There was an identical abnormal DNA index between two aneuploid components.

MD = moderately differentiated; PD = poorly differentiated; WD = well differentiated.

G₀G₁ peak exceeded 10% were not used to determine DNA ploidy of the tumor. Because of this, analysis of DNA ploidy of the adenocarcinomatous component of 1 tumor was not possible, and therefore, DNA ploidy patterns between adenocarcinomatous and squamous carcinomatous components in 12 tumors were compared. The coefficient of variation for the G₀G₁ peak of the diploid and aneuploid cells analyzed ranged from 3.2% to 9.8% (median value, 5.1%) and from 3.9% to 9.4% (median value, 4.7%), respectively. The size of the aneuploid population ranged from 6.3% to 34.1% (median size, 11.8%).

The adenocarcinomatous and squamous carcinomatous components in the same tumor were defined as being related to each other when they showed diploidy or when at least one DNA index of abnormal clones between two aneuploid components was the same or almost identical. The criterion that defined an identical abnormal clone between two aneuploid components was the following: mean DNA index of the subject clones $\times 0.975 < \text{DNA indices of each subject clone} < \text{mean DNA index of the subject clones} \times 1.025$.

Results

The adenocarcinomatous and squamous carcinomatous components in 8 (67%) of the 12 adenosquamous lung tumors were defined as being related to each other. Table 1 shows the DNA ploidy pattern and identical abnormal DNA indices of those components. Both components showed diploidy in 4 tumors. There was an identical abnormal clone between each of the two components in 4 tumors. Figure 1 shows two representative tumors' histologies and the corresponding DNA ploidy patterns.

The relationship between the adenocarcinomatous and squamous carcinomatous components in 4 tumors could not be found using the criteria of the DNA ploidy pattern. As shown in Table 2, the components of squamous cell carcinoma and adenocarcinoma in 3 tumors had DNA diploidy and aneuploidy, respectively. There was a dissimilar abnormal DNA index between two aneuploid components in 1 tumor.

Comment

The histogenesis of adenosquamous lung carcinoma remains unclear. There are many possibilities, including adenocarcinoma with squamous metaplasia, collision tumor, high-grade mucoepidermoid carcinoma, and bipotential undifferentiated cell origin [7, 8]. The study by Steele and Nettesheim [9] shed light on this issue. They examined two different mixed adenosquamous tumors derived from transformed F344 rat tracheal epithelium. The total of 20 clones that had been isolated from the two tumors were cultured and then inoculated into animals for the assessment of in vivo differentiation. Of the 20 single-cell clones, 15, 3, and 2 clones produced adenosquamous carcinomas, adenocarcinomas, and squamous cell carcinomas, respectively. These findings strongly suggest that a mixture of differentiated cell types in adenosquamous cell carcinoma does not result from a mixture of stem cells with one fixed phenotype in the tumor, but rather from instability of differentiation.

The criteria used here to determine the relationship between adenocarcinomatous and squamous carcinomatous components in the same tumor by DNA flow cytometry are based on the following two hypotheses: (1) In the case of both being diploid components, there are no

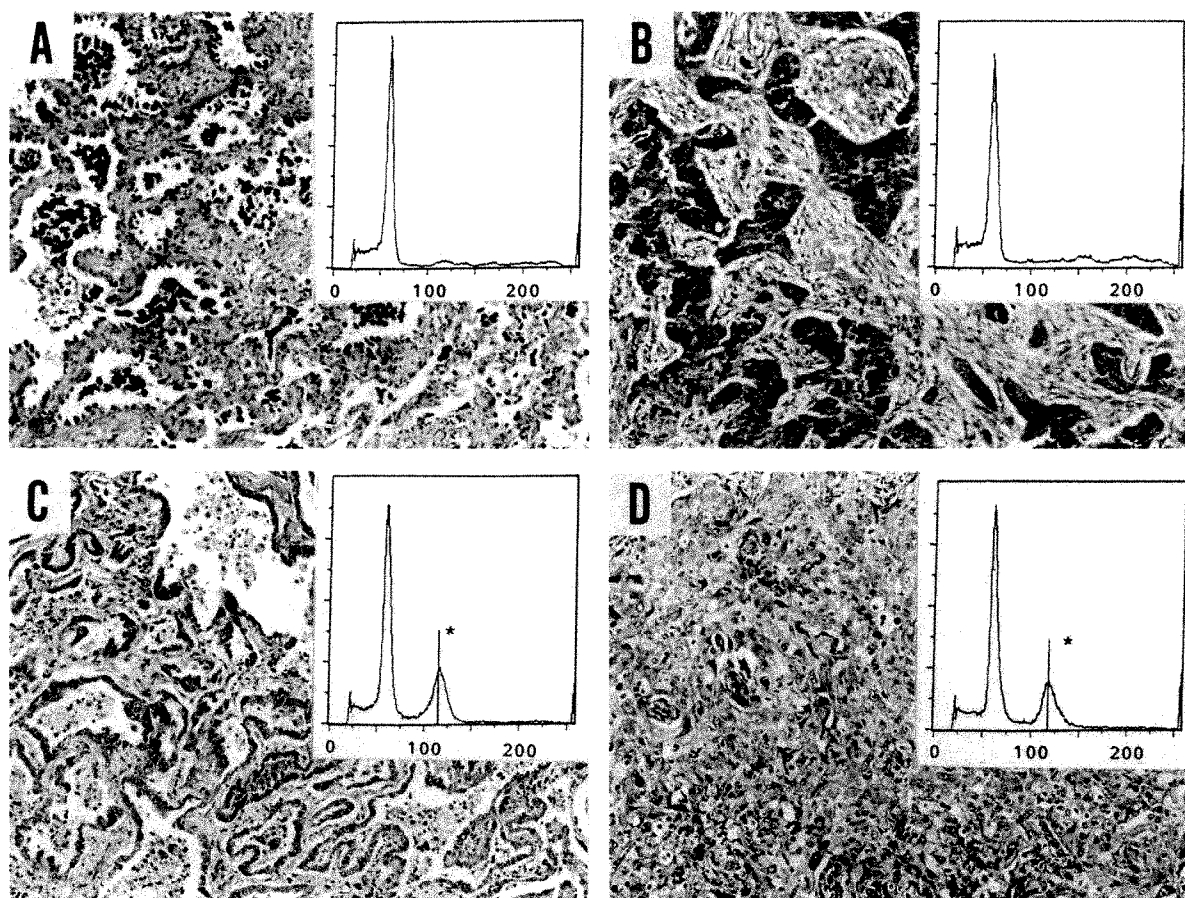


Fig 1. Histologic features and histograms of DNA flow cytometry of adenocarcinomatous and squamous carcinomatous components in surgically resected adenosquamous lung carcinoma. The abscissa and the ordinate in DNA histograms represent relative DNA fluorescence intensity and cell number, respectively. Histologically, patient 1 (see Table 1) had (A) well-differentiated adenocarcinoma and (B) moderately differentiated squamous cell carcinoma. Both components had DNA diploid patterns. Histologically, patient 8 (see Table 1) had (C) well-differentiated adenocarcinoma and (D) moderately differentiated squamous cell carcinoma. (All, hematoxylin and eosin; $\times 100$.) (* = identical abnormal DNA clone between two components.)

abnormal clones in terms of DNA ploidy, and thus their biological characteristics can be considered similar, and (2) when at least one DNA index of abnormal clones between two aneuploid components is the same or almost identical, both components can be thought to be related, in part, to each other. Our recent studies [10, 11] have shown that these criteria work for identifying the relationship between pulmonary metastases or recurrent tumors and primary tumors.

In the present study, we were able to demonstrate similar biological characteristics, in terms of DNA ploidy patterns, between the adenocarcinomatous and squamous carcinomatous components in 8 (67%) of the 12 adenosquamous lung carcinomas. The figure of 67% could be considered too high if adenosquamous carcinomas were composed of different stem cells. Therefore, this observation may lend support to the conclusion of Steele and Nettesheim [9].

The survival of patients who undergo surgical resection of adenosquamous lung cancer is variable [2, 12, 13]. In

Table 2. Summary of Data on Tumors With Dissimilar DNA Ploidy Pattern

Patient No.	Pathological TNM Stage	Diploid Component or DNA Index in Aneuploid Component		Survival After Operation (mo)
		Adenocarcinoma	Squamous Cell Carcinoma	
1	T2 N0 M0	MD (50) ^a 2.085	PD (50) Diploid	Died, 34
2	T2 N2 M0	MD (20) 1.746	MD (80) 1.932	Died, 14
3	T2 N2 M0	MD (40) 1.534	MD (60) Diploid	Died, 26
4	T3 N1 M1	WD (50) 2.103, 2.466	PD (50) Diploid	Died, 17

^a Numbers in parentheses are percentages of largest cut surface area of tumor occupied by component.

MD = moderately differentiated; PD = poorly differentiated; WD = well differentiated.

our series, the 5-year survival rate is 20% for the 5 patients in pathological stage I, which is poor compared with that of patients with adenocarcinoma or squamous cell carcinoma. However, 3 of the 4 patients in whom both adenocarcinomatous and squamous carcinomatous components showed diploidy have survived 124 months (stage I), 50 months, and 16 months (both stage III) after operation. Whether analysis of DNA flow cytometry of the tumor is capable of identifying which patients with adenosquamous lung cancer have a good prognosis, as shown in adenocarcinoma or squamous cell carcinoma of the lung [14-16], should be investigated in the future.

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Recycling of the Internal Mammary Artery in Coronary Reoperation

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In 5 patients undergoing a coronary artery reoperation, the internal mammary artery graft was taken down and reused. No special problems were encountered perioperatively or postoperatively. Because the number of grafts and distal anastomoses performed in coronary reopera-

tions is increasing, lack of suitable graft conduits will be a problem in the future. Recycling an internal mammary artery graft may be an option to achieve good revascularization in some coronary reoperations.

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Over the years, the number of grafts and distal anastomoses at reoperation has increased, whereas suitable graft material is limited [1]. The use of one internal mammary artery (IMA) or both IMAs in primary coronary operations leaves more saphenous vein available at reoperation. However, using IMAs in coronary reoperations provides more latitude in graft conduits [2]. With previous use of the IMAs as grafts, however, the specific problem of lack of bypass conduits can arise. Several alternatives to the great saphenous vein were tried, but the results were poor [3]. Recently, we have reused the left IMA (LIMA) in five coronary artery reoperations. Here we describe and discuss our experience with the "recycled" IMA in coronary artery reoperations.

Material and Methods

Patient Population

Between January 1987 and December 1991, 206 coronary reoperations were performed in our department. In 9 patients, the LIMA, the right IMA (RIMA), or both had already been used as grafts. In 5 patients (3 men, 2 women), we reused the LIMA at reoperation.

Preoperatively all 5 patients were in New York Heart Association functional class III. The mean age at reoperation was 63 ± 8 years (range, 58 to 70 years), and the mean interval between the first operation and reoperation was 51.6 ± 28.1 months. All patients had a family history of atherosclerotic heart disease, 4 had a history of smoking after the first operation, and 1 had insulin-dependent diabetes mellitus.

In 4 patients, the angiographic indication for reoperation was progression of atherosclerosis in the native coronary vessels and the venous grafts. One patient had an isolated graft failure, namely, a stenotic IMA graft to the left anterior descending coronary artery (LAD). This patient underwent reoperation 10 months after the first operation. The indication for takedown and reuse of the

LIMA graft to the LAD was a stenotic LAD anastomosis in 1 patient, a new stenosis distal to the previous anastomosis in 1, damage to the pedicle near the distal anastomosis during dissection of the IMA pedicle in 1, and the absence of suitable bypass conduits in 2 patients.

Surgical Technique

The sternum was opened with an oscillating saw, and the aorta and the right atrium were dissected free. The RIMA was harvested synchronously with the appropriate length of large saphenous vein if it was necessary and available. After adequate heparinization, the ascending aorta was cannulated, and a two-stage cannula was inserted into the right atrium for venous return. A left ventricular vent was inserted through the right superior pulmonary vein.

The patient was cooled to a core temperature of 30°C , and the used LIMA was carefully dissected, starting close to where it entered the pericardium. When it was possible to clamp the LIMA, the patient was cooled to a core temperature between 26° and 28°C , and slushed ice was used as topical cooling. When the heart fibrillated, the LIMA was clamped and infusion of cardioplegia started. Cold (4°C) St. Thomas' Hospital cardioplegia was delivered antegrade (3 patients) or retrograde (2 patients) through the coronary sinus coronarius cannula [4] until asystole occurred; cardioplegia was maintained by reinfusion of 100 mL/m^2 every 25 to 30 minutes or earlier if needed.

At the time of asystole, the LIMA-pedicle was further dissected. The distal anastomoses were done during a single period of aortic cross-clamping, and the proximal anastomoses were performed using a partial occluding clamp. Before the patient was weaned from extracorporeal circulation, he or she was rewarmed to a rectal temperature of 35°C , and hematocrit was increased to a minimum value of 0.24.

Results

The used LIMA was reimplanted into the LAD in 3 patients. In 1 of them, the stenotic anastomosis of the LIMA to the LAD was reconstructed. In the patient with

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a new stenosis in the LAD just distal to the first LIMA-LAD anastomosis, the initial anastomosis was taken down, the incision in the LAD was extended over the new eccentric lesion, and a new LIMA-LAD anastomosis was constructed. The patient with a patent LIMA graft to the LAD received a RIMA graft to the first marginal branch and a venous graft side-to-side to the second marginal branch of the circumflex coronary artery ending on the distal right coronary artery. During the reoperation, a hematoma, probably resulting from the dissection, formed near the LIMA-LAD anastomosis and led to the need to reconstruct this anastomosis.

In 2 patients, there was a lack of good venous conduit material. One was a woman with extensive varicose veins. The patent LIMA-LAD graft was taken down, and the LIMA was anastomosed to the first and second marginal branches of the circumflex coronary artery. With the RIMA, a RIMA-LAD anastomosis was constructed. The RIMA in situ was not long enough to reach the circumflex coronary artery. In the last patient, adhesions prevented placement of the RIMA through the transverse sinus. The patent LIMA was used to construct a graft to the marginal branch of the circumflex coronary artery, the RIMA was used as graft to the LAD, and saphenous vein served as a graft to the distal right coronary artery. In these 2 patients, use of a free RIMA graft was rejected because of a thickened aorta.

Postoperatively there was no evidence of perioperative myocardial infarction. At follow-up ranging from 5 months to 4 years after reoperation, all patients are in New York Heart Association class I. Four patients had a negative treadmill test at the postoperative reevaluation. The fifth patient, a woman 70 years old, did not attend the reevaluation sessions. No control arteriograms were available because there was no medical indication for postoperative catheterization.

Comment

The number of reoperations for myocardial revascularization is increasing. Whereas the first reoperations were necessary because of progression of atherosclerosis in the native coronary system or an incomplete primary revascularization, graft failure and the combination of graft failure and progression of atherosclerosis are the most important angiographic indications for reoperation. Consequently, there are an increasing number of distal anastomoses at reoperation but a limited supply of suitable graft material.

In patients who received only venous grafts at the first operation, the rest of the saphenous vein as well as both IMAs are available at reoperation [2]. In more and more patients, however, the LIMA will be used as a graft to the LAD at the initial operation. Despite the superior patency rate of the IMA grafts and their good results in reducing angina [5], progression of atherosclerosis will occur in these patients in the native coronary system and venous grafts. In addition, widespread use of the IMA as a graft to relatively badly diseased coronary arteries will lead to a lower patency rate and an earlier return of angina. Use of

IMA grafts at the first operation leaves more large saphenous vein for reoperation, but in some patients, the usable saphenous vein in combination with the RIMA will not be sufficient for a complete revascularization.

Results with the use of upper extremity veins [6], allogenic veins [7, 8], and synthetic conduits [9] as graft material are disheartening, as are the results with the radial artery [10]. The use of the gastroepiploic artery and the epigastric artery as conduits in coronary reoperations has occasionally been reported but is not common [11]. Placing a free IMA graft during reoperations has been reported [2], but the anastomosis of the IMA to the thickened aorta can compromise patency, already lower than that of an in situ IMA graft [5]. An alternative is to redo the revascularization procedure and reuse the IMA graft in another place.

It is known that IMAs are nearly free from atherosclerosis and that there is a low incidence of atherosclerosis in IMA grafts over a long period [5, 12, 13]. At this time, there is no contraindication to the reuse of a patent IMA graft. Nevertheless, the takedown of a patent graft reflects an incomplete revascularization or a revascularization with inferior conduits.

Preoperative angiography of the used LIMA is essential to exclude stenoses in this graft, and it is helpful to have an idea of the position of the LIMA pedicle. This can be important for the dissection of the pedicle. Identification of the IMA pedicle is crucial; once the IMA pedicle is identified, further dissection to mobilize it is not a great problem. Dissection of the IMA pedicle is necessary because the IMA has to be clamped not only to ensure optimal myocardial protection by infusion of cardioplegia but also to manipulate the heart. Lack of good bypass conduits is a subjective indication, as every surgeon has his or her own ideas and criteria about what constitutes an inferior conduit. Nevertheless, with the evolution of the angiographic indications for reoperation and with the increasing number of repeat coronary reoperations [1], the lack of suitable graft conduits will be a problem in the future. Every reoperation will be a challenge where the creativity of the surgeon will be important.

Our initial experience with recycling of the LIMA graft is good. We reused the LIMA in 2 patients because there was a lack of good bypass conduits. In the other 3 patients, the indication for recycling the LIMA was not related to the absence of suitable bypass conduits (in 1 it was due to a perioperative injury), but their cases demonstrate that recycling an IMA graft is a possible alternative.

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Notice From the Southern Thoracic Surgical Association

The Fortieth Annual Meeting of the Southern Thoracic Surgical Association will be held at Marriott's Bay Point Resort, Panama City Beach, Florida, November 4-6, 1993. The Postgraduate Course will be held the morning of Thursday, November 4, 1993, and will provide in-depth coverage of thoracic surgical topics selected primarily as a means to enhance and broaden the knowledge of practicing thoracic and cardiac surgeons.

Members wishing to participate in the Scientific Program should submit an original abstract and one copy by May 15, 1993, to Harvey I. Pass, MD, Program Chairman, Southern Thoracic Surgical Association, 401 North Michigan Avenue, Chicago, IL 60611-4267. Abstracts must be submitted on the Southern Thoracic Surgical Association abstract form. These forms may be obtained from the Association's office or in this issue of *The Annals of Thoracic*

Surgery. Manuscripts of accepted papers must be submitted to *The Annals of Thoracic Surgery* prior to the 1993 meeting or to the Secretary-Treasurer at the opening of the Scientific Session.

Applications for membership should be completed by July 1, 1993, and forwarded to Marion R. Lawler, MD, Membership Committee Chairman, Southern Thoracic Surgical Association, 401 North Michigan Avenue, Chicago, IL 60611-4267.

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Anomalous Course of the Left Brachiocephalic Vein

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An anomalous course of the left brachiocephalic vein beneath the aortic arch was identified in 7 patients undergoing surgical repair of congenital cardiac malformations. Six of these patients had the morphologic features of tetralogy of Fallot including severe obstruction to the right ventricular outflow tract and a right aortic arch. A review of the literature reveals this to be an uncommon anomaly. When it is present, however, it is frequently associated with a ventricular septal defect,

obstruction of the right ventricular outflow, and aortic arch anomalies. This anomaly can be documented by echocardiography, at cardiac catheterization, or intraoperatively. The presence of a subaortic left brachiocephalic vein may have implications for the conduct of surgical procedures, especially in the setting of tetralogy of Fallot.

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Usually, the left brachiocephalic (innominate) vein courses anterior to the aortic arch and its brachiocephalic branches and joins the right brachiocephalic vein to form the superior caval vein (Fig 1). Rarely, the left brachiocephalic vein has an anomalous course beneath the aortic arch, where it then joins the superior caval vein between the azygos vein and the superior cavoatrial junction. Kershner [1] first described this anomaly in 1888, and it has been reported in the literature only occasionally since then. In this report we describe a series of patients diagnosed at the time of congenital heart operation, review the current literature, and comment on the potential clinical implications of this anomaly.

Patients and Methods

Seven patients undergoing repair of congenital cardiac malformations between September 1987 and June 1991 were found to have the left brachiocephalic vein coursing beneath the aortic arch at the time of operation. One patient was found to have a type B interrupted aortic arch with ductal continuity to the descending thoracic aorta. There was an anomalous origin of the right subclavian artery from the descending thoracic aorta just proximal to the left subclavian artery (Fig 2). In addition, this patient had an aortopulmonary window and an atrial septal defect within the oval fossa.

In the remaining 6 patients, the heart had the morphologic features of tetralogy of Fallot, and all of these had a right aortic arch (Fig 3). Five required a patch across the junction between the right ventricular outflow and the pulmonary trunk because of severe pulmonary stenosis. One patient had an adequately sized pulmonary valve and pulmonary trunk but required a patch confined to the right ventricular outflow tract. One patient had previ-

ously undergone placement of a left modified Blalock-Taussig shunt, and bilateral modified Blalock-Taussig shunts had been constructed in another patient before complete repair. Associated anomalies (Table 1) included one atrial septal defect within the oval fossa, one persistent left superior caval vein, and trisomy 21, and Cornelia-deLange syndrome in 1 patient each.

During this same period, 27 additional patients with tetralogy of Fallot underwent corrective operation. Twenty-one of these patients had a left aortic arch, whereas 6 had a right aortic arch. Seventeen required enlargement of the right ventricular outflow tract with a patch, and in 12 of these the patch extended across the ventriculopulmonary junction (the "annulus"). Two patients had a persistent left superior caval vein, in 1 of whom the left brachiocephalic vein was absent. In the remaining 26, the left brachiocephalic vein took its usual course.

Review

In the century after the initial description of this anomaly by Kershner [1], isolated cases have been reported. In 1985, Smallhorn and colleagues [2] analyzed 7 cases diagnosed by echocardiography. Gerlis and Ho [3] summarized these earlier reports in 1989 and added 3 autopsy cases of their own. Since then, others [4-6] have reported additional cases, all diagnosed by echocardiography. Together, as far as we are aware, a total of 58 cases have been documented, including the 7 cases in this report. Of these cases, only 8 were isolated anomalies with otherwise normal hearts, and all 8 were in male patients with left aortic arches.

In the 44 cases in which the sex of the patient is known, males outnumber females by a ratio of 2.1:1. Including only those cases with malformed hearts, the sex ratio is 1.6:1. The most frequently associated anomalies are those also commonly associated with tetralogy of Fallot, namely, right aortic arch, ventricular septal defect, and

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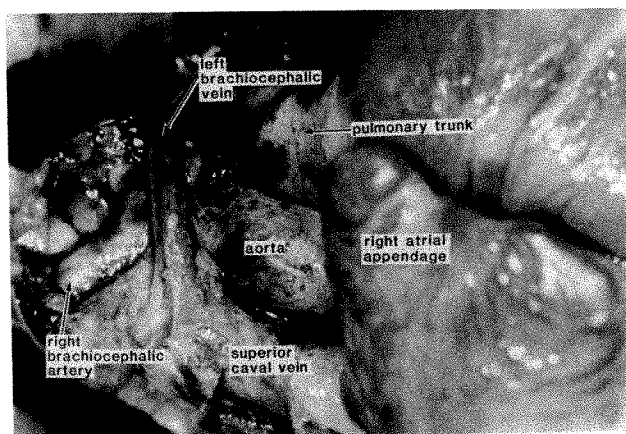


Fig 1. Normal appearance of the left brachiocephalic vein.

obstruction of the right ventricular outflow tract. Of the 24 patients reported by Choi and associates [6], 20 had either tetralogy of Fallot, or pulmonary atresia in the setting of tetralogy. Of these 20 patients, 13 had right aortic arches, as did all 6 of our patients with tetralogy of Fallot. Other associated anomalies included common arterial trunk (2 patients), complete transposition (1 patient), interruption of the aortic arch (1 patient), and multiple complex anomalies (2 patients).

In the majority of cases, the subaortic brachiocephalic vein was noted to course anterior to the arterial ligament or a patent arterial duct. In a few cases, the brachiocephalic vein coursed either posterior to the ligament or behind the pulmonary trunk [3]. In all 7 of our patients, the left brachiocephalic vein coursed anterior to the arterial duct or its ligamentous vestige.

The exact incidence of this anomaly is unknown. Gerlis and Ho [3] estimated it to be 1 in 500 patients, based on the combined collections of approximately 2,000 hearts at their institutions and their review of previous case reports. Choi and associates [6] found an incidence of 1 in

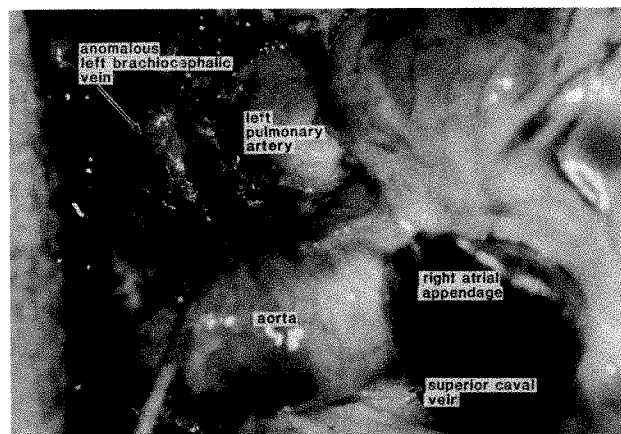


Fig 3. Anomalous course of the left brachiocephalic vein in the patients with tetralogy of Fallot.

100 patients in their review of 2,457 echocardiograms of patients with congenital heart disease. Given the difference in methods used for diagnosis, an accurate determination of the prevalence is difficult. As there does not appear to be any pathophysiologic consequence of this anomaly, it may well go undetected in patients with otherwise normal hearts. It could also escape notice in the routine evaluation of patients with congenitally malformed hearts, thus leading to an underestimation of its true incidence.

Comment

Although of interest anatomically, the subaortic position of the left brachiocephalic vein is physiologically inconsequential. With echocardiography, it is most easily seen using suprasternal long-axis projections. Radiologically, the anomaly can be documented when catheters are placed in both the brachiocephalic vein and the aorta, or when contrast injection is made in the left brachiocephalic vein. Careful postmortem examination can also identify the anomaly.

The preoperative diagnosis of this anomaly should prompt a thorough search for the presence of obstruction

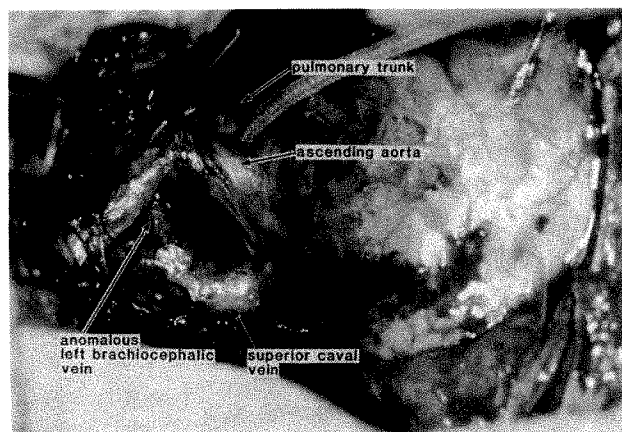


Fig 2. Anomalous course of the left brachiocephalic vein in the patient with type B interrupted aortic arch (patient 1).

Table 1. Patient Characteristics

Patient	Age ^a	Sex	Diagnosis	Associated Anomalies
1	3 days	M	IAA	APW/ASD
2	50 mo	F	TOF	R aortic arch/PFO
3	6 mo	F	TOF	R aortic arch/ASD/LSVC
4	24 mo	M	TOF	R aortic arch/Cornelia-deLange syndrome
5	19 mo	F	TOF	R aortic arch/trisomy 21
6	55 mo	M	TCF	R aortic arch/PFO
7	24 mo	M	TCF	R aortic arch

^a Age at time of operation.

APW = aortopulmonary window; ASD = atrial septal defect; IAA = interrupted aortic arch; LSVC = left superior caval vein; PFO = patent foramen ovale; R = right; TOF = tetralogy of Fallot.

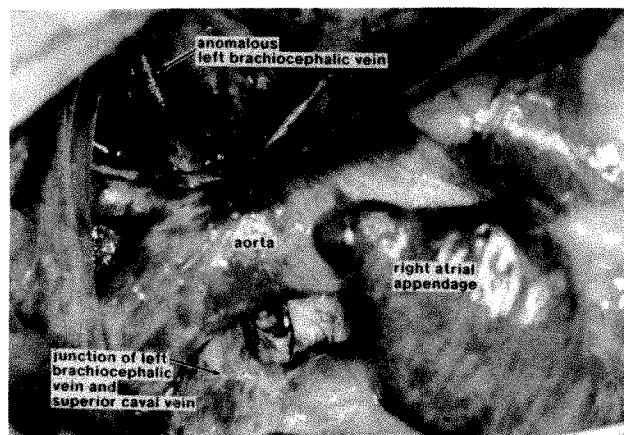


Fig 4. Connection of the anomalous brachiocephalic vein at the superior cavoatrial junction.

within the right ventricular outflow tract, a ventricular septal defect, and a right aortic arch. Conversely, when the diagnosis is made of tetralogy of Fallot with pulmonary stenosis or atresia, the anomalous position of the left brachiocephalic vein beneath the aortic arch should be considered, especially in those patients with a right aortic arch. Recognition of this anomaly may avoid its confusion with the presence or absence of central pulmonary arteries in pulmonary atresia, or a venous confluence in totally anomalous pulmonary venous connection [3].

We identified this entity at the time of median sternotomy for the repair of congenital heart lesions. Its identification has several important implications. Upon initial exploration through a median sternotomy, one might mistakenly conclude that the left brachiocephalic vein is absent. This would suggest the presence of a persistent left superior caval vein, which carries implications for the establishment of adequate venous drainage in the circuit used for cardiopulmonary bypass. Of course, with a subaortic brachiocephalic vein, additional cannulation of the left superior caval vein is not necessary. Because of the anomalous entry of this vein at the superior cavoatrial junction (Fig 4) as opposed to the normal more distal connection, the use of direct cannulation of the superior caval vein must be done with extreme care to avoid obstruction of the left brachiocephalic vein by the venous cannula or damage to the adjacent sinus node or its blood supply. Another situation in which this anomaly might affect surgical technique is in the construction of a bidirectional Glenn shunt as part of a Fontan-type procedure. When performing systemic-to-pulmonary anastomoses,

the presence of this anomaly may also complicate exposure of the pulmonary arteries. Finally, a subaortic left brachiocephalic vein may complicate the exposure and ligation of a patent arterial duct.

Noteworthy is the fact that all 6 patients in this series with tetralogy of Fallot and an anomalous left brachiocephalic vein had a right aortic arch, whereas only 6 of 27 patients (22%) without the anomalous vein had a right aortic arch. This latter percentage is consistent with the accepted incidence of right aortic arch in tetralogy of Fallot of 25% [7].

Of particular interest in these patients with tetralogy of Fallot is the high incidence of relatively severe obstruction in the right ventricular outflow tract. All 6 patients were found to require enlargement of the outflow tract, with patches across the ventriculopulmonary junction in 5. This is in contrast to the finding that 17 of the 27 patients (63%) without the anomalous left brachiocephalic vein required placement of a patch in the outflow tract, with only 12 of these crossing the ventriculopulmonary junction. This anomaly thus appears to be associated with a greater degree of obstruction in the right ventricular outflow tract, and its presence should alert the surgeon to the possible need for a more extensive procedure to accomplish a satisfactory repair. Although this systemic venous anomaly is relatively uncommon, knowledge of it has potentially important implications in the surgical care of patients with congenitally malformed hearts, especially in the setting of tetralogy of Fallot.

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Primary Repair of Iatrogenic Thoracic Esophageal Perforation and Boerhaave's Syndrome

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Ten patients seen at our unit over a 24-month period with either iatrogenic ($n = 5$) or spontaneous thoracic esophageal perforations ($n = 5$) were retrospectively reviewed. Five patients were seen within 24 hours of onset of symptoms, and 5 were seen after 24 hours or later. There was no significant difference in the presentation or subsequent clinical course in patients seen less or more than 24 hours after the onset of symptoms. Nine patients underwent primary repair together with drainage of the mediastinum, and in 1 of these a Heller's myotomy was also performed for achalasia. One patient had a two-stage esophagogastrectomy for a benign esophageal stricture. One patient (10%) with a spontaneous perforation died 48 hours after operation and was found at postmortem examination to have an in situ carcinoma at the site

of the perforation. Four patients (40%) had nonfatal complications. Fistulas developed in 3 patients (30%); in 1 of these patients a second thoracotomy and a further rib resection was required for drainage of a mediastinal abscess. An esophagocutaneous fistula and a persistent mediastinal abscess developed in 1 patient (10%) and necessitated two further thoracotomies for effective drainage. The mean hospital stay was 38.4 ± 25.4 days (range, 16 to 76 days). The findings of this study suggest that primary repair combined with a drainage procedure is the treatment of choice for patients with a perforated intrathoracic esophagus, including those seen more than 24 hours after the onset of symptoms.

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Despite advances in the treatment of esophageal perforations over the last three decades, the mortality remains high [1, 2]. The anatomical location of the esophagus predisposes the patient to the development of fatal mediastinitis and multisystem organ failure if the perforation remains unrecognized. The diagnosis may be delayed because esophageal perforation may masquerade as many other clinical disorders [3]. Boerhaave's syndrome has the highest surgical mortality [4], and this has been related to the barogenic nature of the rupture with wider mediastinal and pleural contamination.

Over recent years, we have adopted a more aggressive surgical policy for the management of iatrogenic perforations for benign disease and Boerhaave's syndrome. We present our results over a 24-month period for 10 consecutive esophageal perforations.

Patients and Methods

The hospital charts of 10 patients treated for esophageal perforation after instrumentation or occurring spontaneously between July 1989 and July 1991 were reviewed. Patients who had perforation with known malignancies were excluded, because the management of malignant perforations has been previously reported by us [5]. The preoperative and postoperative courses were analyzed

and factors identified that contributed to morbidity or mortality.

When first seen all patients were resuscitated by insertion of a central venous line and commenced on a regimen of intravenous antibiotics (cefotaxime, metronidazole, and ampicillin) and fluid. A barium swallow was performed in all patients on arrival to our unit, unless performed by the referring center.

Table 1 provides the clinical details of 10 patients; 5 patients had iatrogenic perforations and 5 perforations occurred spontaneously. In 4 patients who underwent esophagoscopy, the investigation was for dysphagia. One of these patients (patient 9) had a long history (10 years) of dysphagia, and from previous investigations was known to have a benign stricture at 25 cm. Because of her chronic history of dysphagia, when an iatrogenic perforation occurred during esophagoscopy under general anesthesia, an Ivor-Lewis two-stage esophagogastrectomy was performed rather than simple closure. Subsequent histologic examination of the resected specimen found an esophageal ulcer with pseudoepitheliomatous hyperplasia and proliferation of the squamous epithelium. Another patient in this group had achalasia and underwent a Heller's myotomy.

All the patients with Boerhaave's syndrome had typical presentation with a history of vomiting after eating a meal except for patient 4, whose perforation appeared to be completely painless and without a history of vomiting. One patient in the spontaneous group (patient 10) was thought to clinically have Boerhaave's syndrome, but

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Table 1. Clinical Features and Management of Patients With Iatrogenic Perforations of the Esophagus and Boerhaave's Syndrome

Patient No.	Age (y)	Type of Perforation	Delay to Presentation (h)	Time from Perforation to Operation (h)	Operative Treatment	Outcome
1	55	Iatrogenic: esophagoscopy & dilation	14	22	T & L, G & J	Alive
2	58	Boerhaave	8	14	T & L, G & J	Alive
3	58	Iatrogenic: esophagoscopy & dilation for achalasia	4	31	T & L, G & J, & Heller's myotomy	Alive
4	75	Boerhaave	6.5	12	T & L, G & J	Alive
5	57	Iatrogenic: esophagoscopy & dilation	Immediate	24	T & L, G & J	Alive
6	83	Boerhaave	12	18	T & L, G & J	Alive
7	64	Iatrogenic: esophagoscopy & dilation	72	94	Left thoracotomy, G & J	Alive
8	77	Spontaneous perforation	48	60	T & L, G & J	Died 48 hours postop of septicemia
9	74	Iatrogenic: esophagoscopy & dilation of benign stricture (10-year history of dysphagia)	Nil: during general anesthesia for esophagoscopy	Proceeded to esophagectomy	Two-stage esophagogastrrectomy & J	Alive
10	60	Iatrogenic: esophagoscopy & dilation	12	24	T & L, G & J	Alive

G = drainage gastrostomy; J = feeding jejunostomy; L = mini-laparotomy; T = thoracotomy.

histologic examination of the autopsy specimen found an in situ carcinoma on the edge of the esophageal perforation.

The time delay from the onset of symptoms to arrival at the hospital varied from 0 to 72 hours (mean, 17.7 ± 23.5 hours), but the time from symptoms to operation was 0 to 94 hours (mean, 29.9 ± 27.4 hours), with 5 patients receiving operation at 24 hours or more after the onset of symptoms.

Thoracotomy with oversew of the esophageal perforation with interrupted single-layer polyglactin together with mediastinal drainage was performed in 8 patients. In patient 3 (see Table 1), a Heller's myotomy was also performed at the same time as esophageal repair, because a preperforation diagnosis of achalasia had been made. As outlined above, 1 patient had a two-stage esophagogastrrectomy for iatrogenic perforation of the esophagus after dilation for a benign stricture. All patients underwent a mini-laparotomy for the insertion of a drainage gastrostomy and feeding jejunostomy.

A Gastrografin (Schering Health Care, Burgess Hill, UK) radiocontrast swallow was routinely performed on day 5 postoperatively. If this study was negative for an anastomotic leak, the gastrostomy tube was removed and oral administration of fluids commenced. The jejunostomy tube was clamped off but left in situ for a further 24 hours. At the end of this period, if the patient had

successfully proceeded to a soft diet the jejunostomy feeding tube was also removed. Both the gastrostomy and jejunostomy wounds were allowed to heal by secondary intention. However, in the presence of an anastomotic leak, the gastrostomy and jejunostomy tubes were left in situ for continued gastric diversion and jejunostomy feeding until a repeat radiocontrast swallow could no longer demonstrate anastomotic leakage; this was necessary in 3 of our patients.

Results

The presenting features of the patients with subsequent complications in the intensive care unit are provided in Table 2. No significant difference was found in the presenting features of patients who were seen less than or greater than 24 hours from the onset of symptoms. Seven of the 10 patients were already receiving intravenous broad-spectrum antibiotics at the time of arrival to our unit, and 6 of these patients had metronidazole as part of their antibiotic regimen. The early institution of antibiotics and the use of an antianaerobe may have facilitated the low mortality in our group of patients. There was no significant difference in the intensive care unit course of patients who presented less than or greater than 24 hours after onset of symptoms. The ventilation time for patients in intensive care unit was 0.3 to 7 days (mean, 1.1 ± 2.1

Table 2. Presentation and Intensive Care Unit Complications

Variable	All Patients (n = 10)	>24 Hours (n = 5)*
Presentation		
Pyrexia	4	1
Tachycardia	5	2
Leukocytosis	7	4
Hypotension (<100 mm Hg)	3	2
Shock	1	0
Renal dysfunction	2	1
Hypoxia	6	2
Antibiotic therapy on presentation	4	3
ICU Course		
Hypotensive episodes	3	2
Arrhythmia	2	2
Ionotropes	2	1
Renal dopamine	3	2
Ventilation (>12 hours)	5	3

* Patients seen 24 hours or later after the onset of symptoms.

ICU = intensive care unit.

days). In 1 patient, who was ventilated for 7 days, adult respiratory distress syndrome developed after operation.

After operation persistent leaks demonstrable on Gastrografin swallow developed in 3 patients. In 2 patients leaks were successfully managed by prolonged jejunostomy tube feeding. However, 1 patient required a second thoracotomy for drainage of a paraesophageal abscess. A rib resection was also necessary in the same patient to drain a mediastinal abscess. A persistent esophagocutaneous fistula in this man (patient 4) was successfully healed by endoscopic application of sodium hydroxide to the esophageal ostium of the fistulous tract. A fourth patient without a demonstrable radiological leak required a second thoracotomy for drainage of a mediastinal abscess.

One patient (patient 8) died in this series. She was seen late (60 hours) after the onset of her symptoms and was undergoing therapy with azathioprine and corticosteroids for bullous pemphigoid. Despite the early institution of antibiotic therapy septicemia developed and she died 48 hours after operation. An autopsy found a gangrenous esophagus and necrotizing mediastinitis, with an in situ carcinoma at the edge of the perforation that had not been detected on macroscopic inspection at the time of thoracotomy.

From Table 1 it may be noted that the time from presentation to operation was protracted in some cases, eg, for patient 3 this was 27 hours. This reflects our position as a referral center for these patients. The delay to operation was due to a combination of time taken in establishing the diagnosis at the referring hospital together with time required for transportation of the patient to our unit.

The mean hospital stay was 38.4 ± 25.4 days (range, 16 to 76 days). At discharge all the patients were on a normal

diet without dysphagia. Follow-up was at 6 weeks in an outpatient clinic, at which time 8 of the 9 patients remained well and were discharged; 1 patient was lost to follow-up.

Comment

The management of esophageal perforations remains unclear in the literature because of the heterogeneity of causes and management strategies of reported cases. We have employed a similar technique in 9 of 10 cases presented. In 1 case, esophageal resection was undertaken because of the presence of a benign esophageal stricture. The remaining patients were treated by primary oversew of the perforation and a drainage gastrostomy, except for 1 patient, who also had a Heller's myotomy for achalasia. A feeding jejunostomy was inserted in all patients at the time of primary esophageal repair. This is useful in the postoperative period when prolonged feeding becomes necessary; 2 patients with esophageal leaks were successfully managed by jejunostomy feeding until the leak closed.

It has been suggested that primary closure of the perforation with mediastinal drainage should be reserved for patients seen within 24 hours [6, 7]. Flynn and associates [7] recommended nonoperative treatment for late-presenting perforations, because of infected tissues, which in their view precluded a definitive operation. Although interventional radiological techniques may allow the insertion of a drainage tube through the naso-esophageal, gastroesophageal, or transpleural route [8], this requires radiological expertise, and may still put the patient at risk from a subsequent mediastinal abscess. The alternatives to repair of the perforation are conservative or medical therapy [9], or one of the many drainage or diversion techniques [10-14]. The mortality in a collected series of 80 patients in whom the drainage/diversion technique was used was 35.5% [15], compared with a mortality of 25% for simple repair in a collected series of 158 patients [15]. This latter mortality is an overall mortality; patients with cervical esophageal perforations have a better prognosis [6], whereas those seen late (>24 hours) have a poorer prognosis. Patients with Boerhaave's syndrome in particular have a high mortality of 25% [4], which may be due to the explosive nature of the perforation resulting in wider mediastinal contamination and rapid onset of necrotizing mediastinitis. The 1 patient who died in our study was seen late (48 hours) with spontaneous perforation, but was subsequently found at autopsy to have an in situ carcinoma at the esophageal tear.

The reported frequency of leaks after simple closure after 24 hours is approximately 50% [16-18], with a 39% incidence of fistulas in a collected series of 158 patients [15]. A number of autogenous tissue flaps have been described over recent years to reinforce the repaired esophageal tear [19-21]. Richardson and associates [22] in 1985, reported excellent results with the use of a muscle flap in a small group of 5 patients. The most widely employed technique has been the pleural flap described

by Grillo and Wilkins [21]. In a series of 14 patients, Gouge and associates [15] reported two leaks (14%) but no fistulas. These authors recommended the employment of a buttressing flap in all cases of primary repair. This was supported by the finding of a 13% incidence of fistulas in a collected series of 99 patients who received a number of different buttressing techniques. In our series only one fistula (10%) developed. The low incidence of complications and high survival rate in our series may be due to the high throughput of such cases in our unit. The 10 cases we have reported were seen over a 24-month period, whereas Gouge and associates [15] reported on 14 patients with the Grillo flap treated over 13 years.

Esophagectomy is indicated when underlying esophageal disease may be expected to prevent successful healing of the perforation. At the time of thoracotomy this was missed in 1 of our patients, who subsequently died, but in another patient this was successfully performed because of a benign stricture. We have reported a 36.3% mortality for esophageal resection for perforated esophageal malignancies, whereas all 4 patients who had resections for benign perforations survived [5]. Transhiatal esophagectomy has been recommended for malignant perforations [23, 24]. Yeo and associates [24] performed four transhiatal esophagectomies with cervical esophagostomy without any mortality.

Perforation of the intrathoracic esophagus is a life-threatening condition, and delay in diagnosis and therapy remains a major contributor to the attendant mortality. Few patients fulfill the criteria of Cameron and associates [9] for conservative therapy, ie, the perforation must be contained, the cavity must drain back into the esophagus, and there must be no evidence of sepsis. Drainage or diversion therapy is associated with an unacceptably high morbidity and mortality. Primary repair with a drainage procedure is the treatment of choice in all patients, including those seen more than 24 hours after the onset of symptoms. The use of autogenous tissue buttressing remains controversial. However, the use of the latter technique or indeed the management of this lethal condition is not for the occasional esophageal surgeon. We would recommend referral of patients with esophageal perforations to centers with experience in the management of this condition.

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Cox/Maze Procedure for Atrial Septal Defect With Atrial Fibrillation: Management Strategies

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Atrial fibrillation is found at late follow-up in approximately half of all adults who have had correction of atrial septal defect, even if it was not present preoperatively. These patients are thus exposed to the risks of stroke and chronic drug therapy even after a successful operation. Simultaneous surgical correction of atrial septal defect

and atrial fibrillation was accomplished in a 52-year-old man by means of the Cox/maze procedure. The small added risk and the substantial benefit of eliminating atrial fibrillation suggest that this approach is warranted in selected adults with atrial septal defect.

(Ann Thorac Surg 1993;55:607-10)

Atrial septal defect is the third most common form of congenital heart disease in adults (only bicuspid aortic valve and mitral valve prolapse are more common), and it is frequently associated with atrial fibrillation or flutter [1]. Although the incidence of atrial fibrillation increases with age even in the general population, and ranges from 3.7% of patients older than 65 years to 11.6% of those older than 75 years [2-4], the incidence in patients with atrial septal defect is strikingly higher even after surgical closure [5-7]. In a recent review from the Mayo Clinic of late results 27 to 32 years after surgical repair of isolated atrial septal defect, patients who had closure of an atrial septal defect after age 41 years had a 59% chance of having atrial fibrillation or flutter at late follow-up [1]. For patients who had atrial septal defect closure between the ages of 25 and 41 years, the incidence of late atrial fibrillation or flutter was still 41%, even though only 6% had those arrhythmias preoperatively.

For editorial comment, see page 578.

Several recent studies have demonstrated that atrial fibrillation imposes substantial risks of stroke or death [8-10]. In patients with nonrheumatic atrial fibrillation in the Framingham study [9], the risk ratio for stroke was 5.6 compared with patients without atrial fibrillation, even after adjusting for age and blood pressure. During a 20-year follow-up period, patients in whom atrial fibrillation developed were twice as likely to die as those in whom it did not. This increased risk was attributed in part to their associated heart disease, but also to the excess risk of stroke. In the Mayo Clinic study of atrial septal defects [1], even patients who had closure of an atrial septal defect between the ages of 25 and 41 years had shortened life spans, and those with closure after age 41 years had

an even greater increase in late mortality. Of 35 late cardiac events in the cohort older than 24 years at closure, eight events were strokes and two were transient ischemic attacks.

In patients with normal cardiac function, atrial fibrillation is generally assumed to be well tolerated, but even in those patients there are hazards besides the well-known risks of thromboembolism and anticoagulation. Prospective echocardiographic studies indicate that atrial fibrillation alone can cause left atrial enlargement [11]. A rapid ventricular rate, as may be present in poorly controlled atrial fibrillation, can cause tachycardic cardiomyopathy [12]. Calcium-channel-blocking drugs, which are often used to control the ventricular response in atrial fibrillation, can exacerbate heart failure [13]. Finally, the antiarrhythmic drugs that are used in an effort to prevent atrial fibrillation have well-recognized proarrhythmic effects. Long-term antiarrhythmic therapy increases mortality substantially, even with familiar drugs such as quinidine [14].

A surgical procedure to abolish atrial fibrillation and flutter has been described by Cox [15, 16]. It therefore seemed to us that in selected adult patients it would be beneficial to surgically correct atrial fibrillation simultaneously with closure of isolated atrial septal defects. Several precisely located incisions are made in the atria and then are closed, creating a maze in which the propagating electrical wave fronts are extinguished at the suture lines (Fig 1). The reentrant circuits that maintain atrial fibrillation cannot be sustained because of the electrical refractoriness that follows the propagating wavefronts through the maze. Closure of a secundum atrial septal defect is readily incorporated into the operation, because the standard Cox/maze procedure includes an incision in the atrial septum to interrupt conduction across the fossa ovalis. In patients with a secundum atrial septal defect, the usual septal incision of the Cox/maze procedure is eliminated, and the atrial septal defect is closed with a patch.

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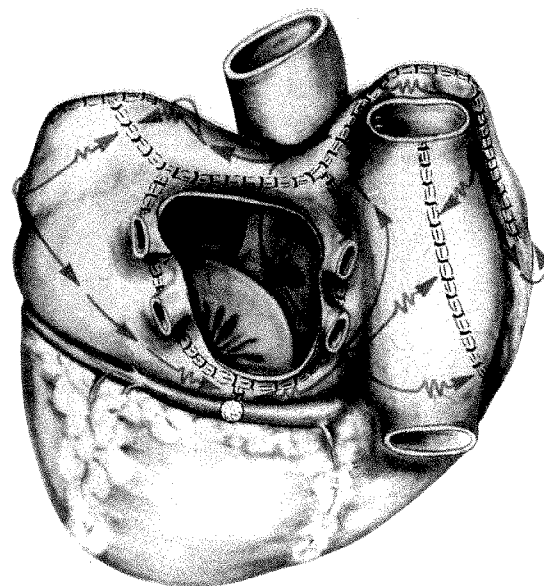
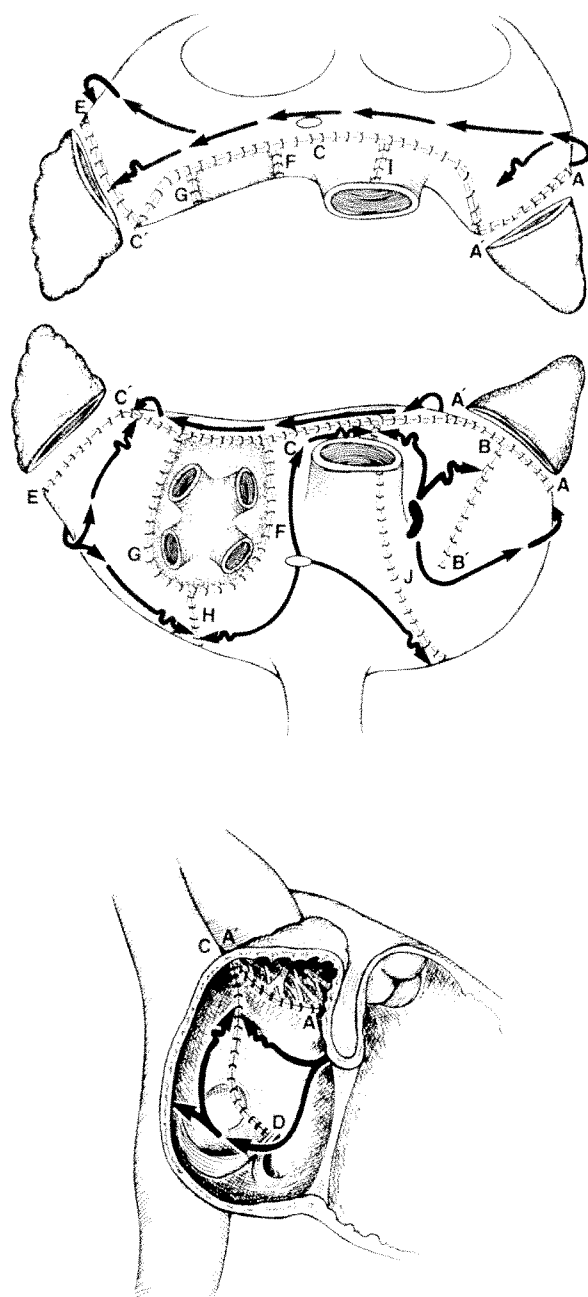


Fig 1. The incisions used for the Cox/maze procedure are displayed in two dimensions (a, b) and three dimensions (c). Propagating electrical wavefronts (black arrows) are extinguished at the suture lines. In the upper left and lower panels, the heart is seen from the posterior view. Incisions A-A' and E-C' depict amputation of the right and left atrial appendages, respectively. (Reproduced from Cox JL, Schuessler RB, Agostino HJ, et al. The surgical treatment of atrial fibrillation: III. Development of a definitive surgical procedure. *J Thorac Cardiovasc Surg* 1991;101:569-83, by permission of Mosby-Year Book, Inc.)

Case History

A 52-year-old man in good general health noted a dry cough, occasional shortness of breath, and episodes of palpitations that increased in frequency, severity, and duration. Evaluation revealed a secundum atrial septal defect with a pulmonary/systemic flow ratio of 2.5:1 and normal pulmonary artery pressure. Atrial fibrillation/flutter alternated with intervals of sinus rhythm. He was referred for surgical closure of his atrial septal defect. After extensive discussions of the risk of simple closure of his atrial septal defect, the risks of atrial fibrillation even

after successful closure of his atrial septal defect, and the risks of the Cox/maze procedure, he elected to undergo the combined procedure.

The Cox/maze procedure was performed uneventfully on July 31, 1991, and the atrial septal defect was closed with a patch of autologous pericardium. The postoperative period was entirely uneventful. Inotropic drugs were not used and blood transfusion was unnecessary. Atrial fibrillation was never observed postoperatively. A visible P wave was noted on the electrocardiogram within 24 hours after operation, with a 1:1 ventricular response.

During the first postoperative week the predominant rhythm was sinus, with long periods of junctional rhythm. (In Cox's patients, junctional rhythm has also predominated early after operation.) A postoperative echocardiogram confirmed closure of the atrial septal defect and contraction of the atria. The patient was anticoagulated for 6 weeks while atrial suture lines healed, and administration of anticoagulants was then stopped. He returned to work as a commercial photographer within 6 weeks. One year postoperatively he remains in sinus rhythm receiving no medications and is asymptomatic.

Comment

Cox has demonstrated the efficacy and safety of the operative procedure he devised for atrial fibrillation. Twenty-six patients have had successful Cox/maze procedures with no deaths (Cox JL; personal communication). The procedure is indeed considerably more intricate and prolonged than simple closure of an atrial septal defect, and requires experience with cryosurgical techniques as well. Cryolesions must be placed wherever macroreentry circuits could propagate along structures that cannot be surgically interrupted: the mitral and tricuspid annuli and the coronary sinus. Nonetheless, although the precise operative risk cannot yet be quantitated, it should be quite low (<2%) in the hands of experienced surgeons, because the operation is confined to the atria, and ventricular function is not affected if proper intraoperative myocardial protection is provided. As the entire procedure is done through the atria, the ventricle can be kept cold within a cooling jacket throughout the period of myocardial ischemia [15, 17]. Our patient did not require any inotropic support postoperatively.

Although catheter techniques for closure of atrial septal defects now show more promise than in the past, long-term follow-up is not yet available, and the technique is suitable only for small to medium defects [18, 19]. It is unlikely that catheter closure will alter the late incidence of atrial fibrillation in patients with an atrial septal defect that becomes manifest in adult life.

Even now, when experience with the Cox/maze procedure is still limited, it seems acceptable to us to consider adding the Cox/maze procedure to routine surgical closure of an atrial septal defect in certain subsets of adult patients. For patients older than 40 years, the likelihood is greater than 50% that atrial fibrillation will develop or be maintained postoperatively [1]. Patients older than 25 years have more than a 40% chance of development of atrial fibrillation. Such patients will require life-long drugs to control their heart rate and rhythm, with the inevitable adverse effects discussed earlier. Patients with atrial fibrillation will also require anticoagulation with warfarin because warfarin markedly reduces their risk of stroke [8, 20, 21].

We therefore propose that the following management guidelines might be considered for adults with atrial septal defect: (1) Patients younger than 25 years with small to medium-sized defects and no arrhythmias should

be considered for catheter closure if the early auspicious reports are confirmed by further experience and late follow-up. (2) Patients younger than 25 years with large defects and no arrhythmias should have surgical closure alone, because the operative risk is negligible and information about late arrhythmias is insufficient to justify a more complex operation with higher risk. (3) Patients older than 40 years with atrial septal defects large enough to require closure, and patients with atrial septal defects and atrial fibrillation/flutter at any age beyond childhood, should have surgical closure and—in experienced centers—consideration of the Cox/maze procedure. This recommendation would not be made in the presence of clinical factors that substantially increase operative risk, such as valvular heart disease or renal failure. (4) Adult patients between the ages of 25 and 40 years with small to medium-sized defects and no arrhythmias can be considered for catheter closure or surgical closure. Surgical closure combined with the Cox/maze procedure may in the future prove to be an appropriate strategy, but at present we lack sufficient information about the risks and long-term benefits of the combined approach in this subset of patients.

In adult patients with atrial septal defects large enough to require operation anyway, the Cox/maze procedure will add a small increment of risk that should be more than counterbalanced by a large benefit. It may also be mentioned parenthetically that there are other circumstances in which atrial fibrillation alone may be an indication for operation [16]. Furthermore, as experience with the Cox/maze procedure increases, and it is done with more certainty and speed, it will surely be combined with more extensive cardiac procedures such as mitral valve reconstruction or replacement in patients with chronic atrial fibrillation and mitral valve disease. Cox has already carried out those combined procedures (Cox JL; personal communication).

We recognize that these proposals require discussion and debate. Many surgeons may disagree on the grounds that these management guidelines are premature and inadequately substantiated. We wish only to document our successful case in the hope that it will provoke consideration of the Cox/maze procedure for patients who might otherwise not benefit from that operation.

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Technique for Resecting Primary and Metastatic Nonbronchogenic Tumors of the Thoracic Outlet

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Although primary or metastatic nonbronchogenic tumors infrequently arise in or involve the thoracic outlet, they represent a major surgical challenge because of their tendency to encapsulate outlet structures. Fourteen patients with a histologically proven primary ($n = 8$) or metastatic ($n = 6$) nonbronchogenic outlet tumor were treated by an anterior transcervical approach, including an L-shaped cervicotomy extended into the deltopectoral groove, resection of the internal half of the clavicle, and, in the case of tumor involvement, resection of the jugular and subclavian veins, phrenic nerve, subclavian artery, brachial plexus, and ribs. All patients underwent a radical resection. Tumors extended to bony (usually the first rib), muscular (usually the anterior scalenus muscle), and nerve (usually the phrenic nerve) outlet structures in 8, 10, and 7 patients, respectively. Ten patients had involvement of outlet vessels: 6 had simple ligation ($n = 5$) or wedge resection ($n = 1$) of the subclavian vein

and related branches, 1 had revascularization of both the subclavian vein by an end-to-end anastomosis and the subclavian artery by a ringed polytetrafluoroethylene graft, 1 had revascularization of the subclavian artery alone, and 2 had revascularization between the left brachiocephalic vein and superior vena cava (ringed polytetrafluoroethylene graft). Follow-up venograms showed complete patency of the anastomoses. There was one postoperative death (7%) due to multiorgan system failure. Other complications were mild and short-lasting. With a median follow-up of 3.4 years, all patients but 1 (who had systemic progression) are alive and disease free 3 to 127 months postoperatively. Radical resection of primary or metastatic nonbronchogenic outlet tumors and encouraging long-term survival can be achieved using the technique presented.

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During the last two decades, the surgical approach to the anterior aspect of the median cervicothoracic junction has been carefully delineated. As a result, surgical procedures for benign and malignant diseases involving the cervical trachea [1], esophagus [2], or both [3, 4] are usually associated with excellent results and low morbidity and mortality. In contrast, the surgical management of neurovascular disorders and malignant diseases involving the thoracic outlet is less well codified, and although various posterior and anterior approaches have been reported, none of them has been widely accepted [5, 6]. This is because the surgical manipulation of structures such as the subclavian artery and vein, phrenic nerve, and brachial plexus is very hazardous and carries a high risk of devastating complications.

Primary and metastatic nonbronchogenic outlet tumors are uncommon neoplasms that may arise from any of the histological elements of this target area. They usually display an aggressive local behavior in that they are deeply infiltrative, and they have a propensity for local

recurrence [7, 8]. Although wide and conservative surgical excision offers the best hope for cure, the frequent encapsulation of outlet structures raises the risk of major injuries, thereby precluding a radical operation. We [9] previously documented the technical feasibility and efficacy of obtaining radical resection of bronchogenic tumors involving extensively the structures of the thoracic inlet by an anterior transcervical approach. Here we present our anecdotal experience with this approach for primary and metastatic nonbronchogenic outlet tumors.

Material and Methods

Between April 1981 and January 1992, 14 patients (6 male and 8 female) with a median age of 44 years (range, 3 to 66 years) with a histologically proven primary ($n = 8$) or metastatic ($n = 6$) nonbronchogenic outlet neoplasm were referred to our institution. Their preoperative demographic profile is shown in Table 1. The primary tumors included 1 Ewing's sarcoma of the first rib, 2 neurofibromas (schwannomas), 2 low-grade fibrosarcomas, 1 fibroma, and 2 radiation-induced fibrosarcomas. The metastatic lesions originated from 1 malignant melanoma of unknown origin, 1 ovarian cancer, 1 testicular teratoma, 1 thyroid cancer, 1 esophageal cancer, and 1 adenocarcinoma of unknown origin. Both radiation-induced fibro-

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Table 1. Demographic Profile

Patient No.	Sex	Age (y)	Tumor Origin	Tumor Type	Tumor Extension	Side	Signs and Symptoms	Preoperative Diagnosis	Previous Local Treatment
1	F	27	Primary	Anterior	Thoracic outlet, mediastinum axilla	Left	Local mass	Schwannoma ^a	Incomplete resection
2	F	59	Primary	Posterior	Thoracic outlet, intraspinal extension (T3-4)	Left	Horner's syndrome	Schwannoma	None
3	F	21	Primary	Posterior	Thoracic outlet, intrathoracic extension	Right	Cervical mass, pain, upper limb edema	Low-grade fibrosarcoma	Multiple incomplete resections, RT (60 Gy)
4	F	50	Primary	Posterior	Thoracic outlet, subscapular fossa	Right	Pain in neck, upper chest and outer arm, venous distention	Low-grade fibrosarcoma	Multiple resections, RT (60 Gy)
5	M	39	Metastatic	Anterior	Thoracic outlet	Left	Local pain	Melanoma of unknown origin	Multiple resections
6	F	24	Primary	Anterior	Thoracic outlet	Left	Shoulder pain, cyanosis and edema of upper limb, phrenic nerve palsy	Ewing's sarcoma of 1st rib	None
7	F	48	Metastatic	Anterior	Thoracic outlet	Left	Local pain, venous distention	Metastatic ovarian cancer	Incomplete resection, RT (17 Gy), and CT
8	M	28	Metastatic	Anterior	Thoracic outlet	Left	Local pain	Metastatic teratoma from carcinoma of testes	None
9	M	40	Metastatic	Anterior	Thoracic outlet, 1st & 2nd ribs	Right	Pain and paresthesia in C8-T1 root	Adenocarcinoma of unknown origin	None
10	F	66	Primary	Anterior	Thoracic outlet	Right	Pain and paresthesia in C8-T1 root, upper limb edema	RIF (breast cancer operation and RT)	None
11	M	3	Primary	Middle	Thoracic outlet, scapula	Right	Local pain	Fibroma	None
12	M	56	Metastatic	Anterior	Thoracic outlet, 1st and 2nd ribs	Right	Local pain	Thyroid carcinoma	Local resection
13	M	52	Metastatic	Anterior	Thoracic outlet	Right	Upper limb edema	Esophageal cancer	None
14	F	57	Primary	Anterior	Thoracic outlet, clavicle, manubrium, and 1st and 2nd ribs	Right	Local pain	RIF (breast cancer operation and RT)	Claviclectomy, manubrial resection

^a In this patient, schwannoma was associated with von Recklinghausen's disease.

CT = cytotoxic chemotherapy; RIF = radiation-induced fibrosarcoma; RT = radiation therapy.

sarcomas occurred at the margin of the radiation field and were of different histologic type than the original tumor (breast cancer). Seven patients (50%) had undergone unsuccessful surgical attempts to remove the tumor before referral, and among these, 2 and 4 patients were experiencing the second and third local recurrence, respectively.

Preoperative Staging

Preoperative staging included history and physical examination, biochemical profile, chest roentgenography, bronchoscopy, computed tomography of the chest, abdominal ultrasound, bone scan, and cardiopulmonary tests. Neurologic examination, electromyography, and fluoroscopy were done to delineate involvement of the brachial plexus and phrenic nerve by the tumor. Vascular invasion was studied with venous angiography, subclavian arteriography, Doppler ultrasonography, and magnetic resonance imaging.

Anatomic Classification

Based on their anatomic location, outlet tumors were classified as anterior (tumor invading the anterior part of the first rib, sternum, manubrium, subclavian vessels, anterior scalenus muscle, and phrenic nerve), middle (tumor involving the middle part of the first rib and extending high into the middle scalenus muscle), and posterior (tumor located close to the vertebral body and invading the posterior part of the first rib, the lower roots of the brachial plexus, the posterior wall, and branches of the subclavian artery).

Surgical Technique

The surgical technique has been extensively detailed elsewhere [9]. Briefly, one-lung anesthesia with measurement of central venous and arterial pressures and body temperature is necessary. A Foley catheter is inserted. The patient is placed in the supine position with the neck hyperextended and the head turned away from the involved side. An L-shaped cervicotomy is made; the vertical and horizontal branches follow the anterior border of the sternocleidomastoid muscle and the inferior border of the internal half of the clavicle, respectively (Fig 1). Division of the sternal attachment of the sternocleidomastoid muscle allows good exposure of the superior border of the subclavian vessels and permits assessment of the extent and resectability of the tumor. The internal half of the clavicle is removed.

The operative procedure is carried out in three steps: primary dissection of the veins, dissection of the arteries, and exposure of the brachial plexus. The jugular and subclavian veins are dissected first so that branches to the subclavian vein can eventually be divided. On the left side, ligation of the thoracic duct is usually required. Division of the distal part of the jugular vein makes the approach to the venous confluence at the origin of the innominate vein easier. If the subclavian vein is involved by tumor, it can easily be resected after proximal and distal control has been achieved. Direct extension of the tumor to the innominate vein does not preclude resection.

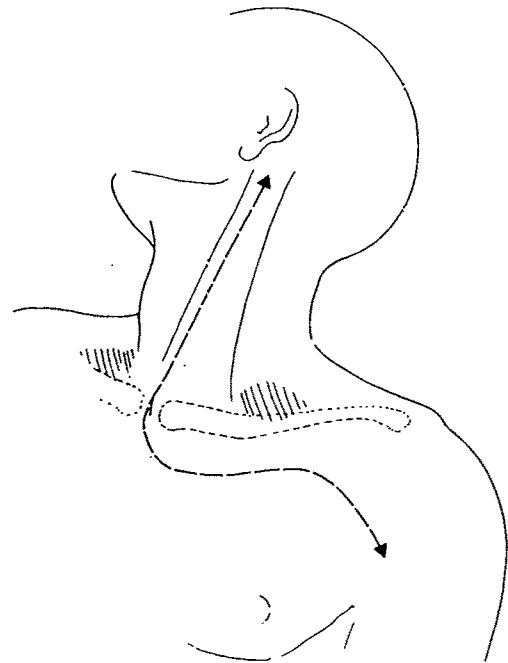


Fig 1. Left transcervical incision: The patient is placed in the supine position with the neck hyperextended and the head turned away from the involved side. An L-shaped skin incision is made from the angle of the mandible down to the sternal notch, extended horizontally under the internal half of the clavicle, and carried into the deltopectoral groove.

The subclavian artery is then dissected: its distal part can be exposed after division of the anterior scalenus muscle over the first rib for tumor-free margins. The phrenic nerve is identified and exposed on the anterior aspect of the anterior scalenus muscle; depending on its tumor involvement, it must be either carefully preserved or resected. The eventual division of branches of the subclavian artery, if invaded by tumor, is simplified after proximal control of its origin is obtained. The internal mammary artery and the ascending cervical artery are often divided, and the vertebral artery, when involved, can also be resected. When the tumor rests against the wall of the subclavian artery, the artery can be freed along a subadventitial plane. Whenever the arterial wall is involved by tumor, resection of the artery to obtain tumor-free margins is necessary; revascularization is performed either with a polytetrafluoroethylene graft (No. 6 or 8) or by end-to-end anastomosis. In middle-type tumors, the middle scalenus muscle can be extensively invaded, requiring its high division for tumor-free margins.

Extension to or compression of the brachial nerves by tumor requires an "out-in side" dissection. Secondary branches and then primary branches of the brachial plexus are freed. The lower trunk and C-8 and T-1 nerve roots can be dissected up to the spinal foramen. Although spread of the tumor to the brachial plexus can be high, neurolysis is usually achieved without need for division of branches of the brachial plexus above T-1.

Exposure of the vertebral body, sympathetic chain, and

stellate ganglion is thereafter easily obtained, and tumor that has spread to these structures can be easily resected. Once structures above the thoracic inlet have been freed from tumor and resected, the first and second ribs or any other adjacent structures, if involved, can be easily resected.

Statistical Analysis

Survival was calculated from the date of operation to death or the date of the last follow-up for patients who remained alive and disease free. Patients were followed up every 6 months by routine chest roentgenograms, computed tomographic scans of the outlet region, and any other necessary procedures already mentioned.

Results

There were ten anterior, three posterior, and one middle outlet tumors. The surgical outcome is detailed in Table 2. There were no operative deaths; 1 patient (patient 12) (7%) died on postoperative day 30 of multiorgan system failure. Two patients experienced complications: mild and short-lasting postoperative motor and sensory deficits in the C5-7 nerve roots in patient 3 and shoulder pain in patient 4.

All patients underwent radical resection of the tumor and the invaded adjacent structure or structures. This was achieved using the anterior cervical approach alone in 10 patients. In the 3 patients with a posterior tumor, the cervical approach was associated with a one-stage posterolateral thoracotomy ($n = 2$) or a median interscapular approach ($n = 1$). A median sternotomy was necessary in 1 patient (patient 12) whose tumor involved the cephalic border of the superior vena cava and in whom a right upper lobectomy was necessary.

Tumors extended to the bony, muscular, and nerve outlet structures in 8, 10, and 7 patients, respectively. Ten patients had tumor involvement of the subclavian vessels. Six of them had simple ligature ($n = 5$) or wedge resection ($n = 1$) of the subclavian vein and related branches, 1 patient had revascularization of both the subclavian vein by an end-to-end anastomosis and the subclavian artery by a ringed polytetrafluoroethylene graft (6 mm), 1 had revascularization of the subclavian artery alone (end-to-end anastomosis), and 2 patients had revascularization between the left brachiocephalic vein and superior vena cava (ringed polytetrafluoroethylene graft, 12 mm). Follow-up venograms showed complete patency of the anastomoses.

Follow-up

With a median follow-up of 3.4 years (range, 3 to 127 months), all but 1 of the operative survivors are alive and without evidence of local recurrence. None of the patients received adjuvant radiation therapy. Patients with benign lesions received no further therapy, and the 2 patients with esophageal cancer and adenocarcinoma of unknown origin were subsequently treated with systemic chemotherapy targeting the primary tumor.

There has been only one late death. Patient 5 died 21

months after operation of systemic progression of metastatic melanoma despite chemotherapy. One patient (patient 3) had local recurrence to the subscapular and trapezius muscles and residual bony scapular structure 17 months postoperatively; he underwent a successful scapulectomy and is alive and disease-free.

Illustrative Case Reports

PATIENT 2. A 59-year-old woman was seen in March 1984 with a 5-month history of a left outlet mass associated with Horner's syndrome. She denied hoarseness, weight loss, arm or shoulder pain, and muscular weakness in the left arm or hand. The results of physical examination were within normal limits. Chest radiography revealed a left apical mass mimicking an apical bronchogenic tumor (Fig 2A). Computed tomographic scan confirmed the cervical location of the mass (Fig 2B) and showed its extension into the posterior mediastinum, where osteolysis of the body of T-4 and enlargement of the corresponding intervertebral foramen (Fig 2C) were discovered. Arteriography of the left humerus demonstrated that the tumor mass was located above the superior margin of the subclavian artery, between the origin of the vertebral artery and the inferior thyroid artery and thyrobrachiocephalic trunk, which appeared dislocated and compressed (Fig 2D). Myelography confirmed an extradural medullar compression. A needle biopsy specimen was positive for schwannoma. Fiberoptic bronchoscopy and extrathoracic workup were negative. Serum laboratory values were normal.

A one-stage anterior cervical and posterior interscapular approach was performed on April 24, 1984. Through a median interscapular incision, the neurosurgeon first performed a hemilaminectomy of T-3 and T-4 with mobilization of the interspinous canal extension of a well-encapsulated tumor. The anterior cervical approach was then performed. Because of the absence of tumor invasion, dissection of all vascular and nerve outlet structures and resection of a well-encapsulated tumor lying on and compressing the superior surface of the subclavian artery and its major branches were easily performed. The patient recovered without sequelae and is alive and disease-free.

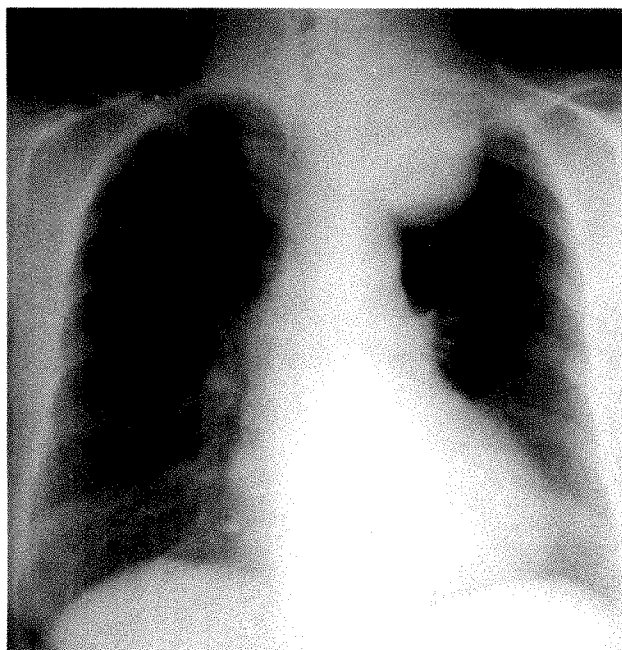
PATIENT 14. A 57-year-old woman was seen in December 1991 with a diagnosis of recurrence from radiation-induced fibrosarcoma of the right thoracic outlet, clavicle, manubrium, and first and second ribs. In January 1978, she underwent total mastectomy for a primary breast cancer; in July 1978, a primary tumor relapse occurred and was treated with bilateral ovariectomy and radiation therapy to the primary and axillary areas. She did well until 1986, when a spontaneous rupture of the internal half of the clavicle occurred, and a diagnosis of radiation-induced fibrosarcoma was made; she underwent a partial right claviculectomy. In February 1991, she experienced a recurrence to the manubrium, and a partial manubrial resection was done. In November 1991, a new recurrence was observed, and she was referred to our institution.

Physical examination revealed a painful 2 × 2-cm mass lying subcutaneously at the right margin of the manubrium and the distal part of the previously resected

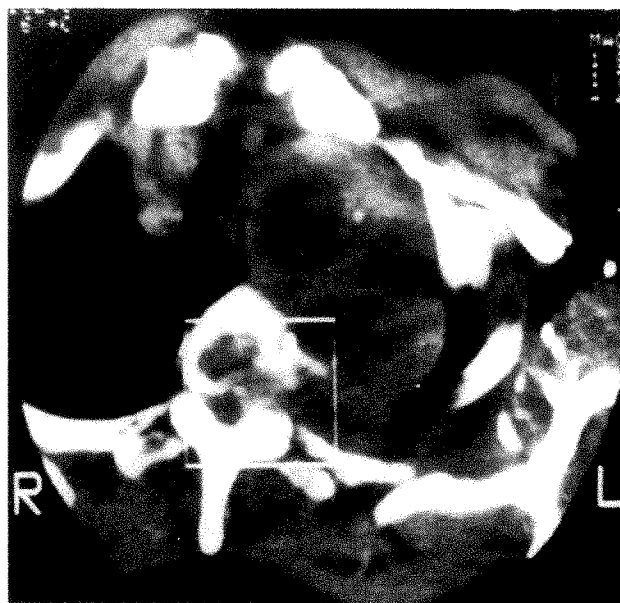
Table 2. Surgical Outcome

Patient No.	Surgical Approach	Involved Bony Structure (s)	Involved Muscle(s)	Involved Nerve(s)	Involved Vessel(s)	Tumor Size (cm)	Status (mo)
1	Cervical	...	...	...	...	3 × 2	Alive (127)
2	Cervical and hemilaminectomy (T-3, T-4)	...	...	...	...	12 × 5 × 4	Alive (95)
3	Cervical and PLT	1st and 2nd ribs	SCM, ASM, 2nd intercostal muscles	PN, middle and lower BP trunks	Ligature of SV and IJV	17 × 8 × 5	Alive (51)
4	Cervical and PLT	1st rib, axillary margin of the scapula	Posterior scalene, trapezius, subscapular and serratus anterior muscles	...	...	6 × 2 × 3	Alive (49)
5	Cervical	...	Minor pectoral muscle	...	...	5 × 2 × 2	Dead (21)
6	Cervical	1st and 2nd ribs	ASM	PN	EEA of SV and artery ^a	12 × 5 × 5	Alive (46)
7	Cervical	1st rib	ASM	PN	Ligature of SV major branches	7 × 3.5	Alive (45)
8	Cervical	...	ASM	...	Ligature of IJV, IMA, and TBCS	6 × 3	Alive (41)
9	Cervical	2nd, 3rd, 4th ribs	Major and minor pectoral muscles	Lower trunk of BP	Ligature of SV; EEA of SA	9 × 1.5	Alive (17)
10	Cervical	...	...	...	Wedge of SV	8 × 2	Alive (8)
11	Cervical + scapulectomy	Rib 1	ASM, MSM, subscapular muscle	...	Ligature of major SA branches except VA	4 × 1.5	Alive (6)
12	Cervical + median sternotomy	1st and 2nd ribs	Major pectoral muscle	PN, vagus nerves	Ligature of SV, IJV, and VA; revascularization of LIV and SVC ^b	4 × 5	Dead (1)
13	Cervical	...	ASM	PN	Ligature of IMA and TBCS	3 × 2	Alive (3)
14	Cervical	1st rib, manubrium	...	PN	Ligature of IMA; revascularization of LIV and SVC ^b	6 × 3	Alive (3)

^a A ringed polytetrafluoroethylene graft (6 mm) was used. ^b The revascularization between the LIV and the SVC was done with a ringed polytetrafluoroethylene graft (12 mm).
 ASM = anterior scalenus muscle; BP = brachial plexus; EEA = end-to-end anastomosis; IJV = internal jugular vein; IMA = internal mammary artery; LIV = left innominate vein; MSM = middle scalenus muscle; PLT = posterolateral thoracotomy; PN = phrenic nerve; SA = subclavian artery; SCM = sternocleidomastoid muscle; SV = subclavian vein; SVC = superior vena cava; TBCS = thyrobricervicoscapular trunk; VA = vertebral artery.



A



C



B



D

Fig 2. (A) Chest roentgenogram showing a left apical mass mimicking an apical tumor. (B) Computed tomographic scan demonstrating a tumor mass of the thoracic outlet extending into the posterior mediastinum and inducing osteolysis of the body of T-4. (C) Computed tomographic scan showing enlargement of the corresponding intervertebral foramen. (D) Arteriogram of left humerus showing that the tumor mass was located in the area above the superior margin of the subclavian artery, between the origin of the vertebral artery and the inferior thyroid and thyrobicervicoscapular arteries; all these vessels appeared dislocated and compressed.

clavicle; she denied superior vena cava signs and symptoms, weight loss, Horner's syndrome, and right arm or shoulder pain. A preoperative computed tomographic scan (Fig 3A) confirmed the mass. The magnetic resonance imaging scan revealed major involvement of the confluence between the right brachiocephalic vein and the superior vena cava; the innominate artery was not in-

volved (Fig 3B). Superior phlebocavography showed stenosis of the caudal part of the right brachiocephalic vein, compression of the superior margin of the terminal part of the left brachiocephalic vein, and rigidity of the cephalic portion of the superior vena cava (Fig 3C).

Definitive resection was performed through an anterior transcervical approach alone. The tumor was 6 × 3 cm in

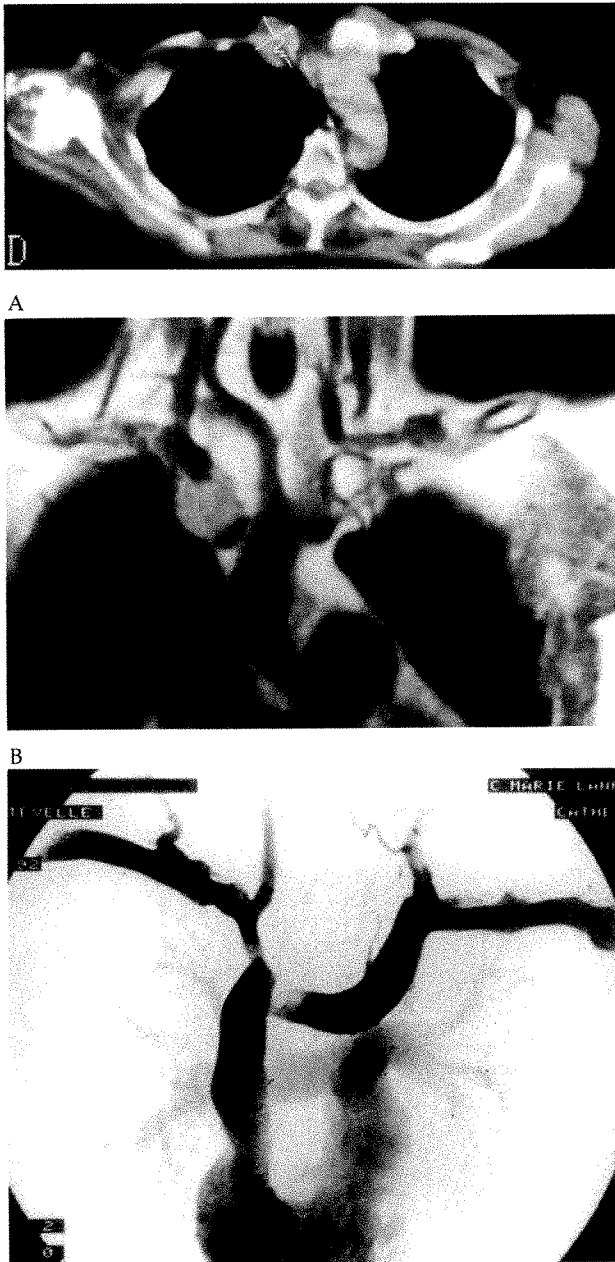


Fig 3. (A) Computed tomographic scan demonstrating a right subcutaneous tumor bulging into the underlying muscles, the right margin of the previously resected manubrium, and the distal part of the previously resected clavicle. (B) Axial magnetic resonance imaging scan showing a tumor 2 cm in diameter originating in the outlet area and extending to the confluence between the right brachiocephalic vein and the superior vena cava, without involving the innominate artery. (C) Phlebocavogram showing stenosis of the caudal part of the right brachiocephalic vein, compression of the superior margin of the terminal part of the left brachiocephalic vein, and rigidity of the superior portion of the superior vena cava.

diameter and extended proximally to the periosteum of the previously resected internal half of the clavicle, the caudal portion of the subclavian vein, the right brachiocephalic vein, the cephalic portion of the superior vena

cava, first rib, manubrium, and visceral pleura; distally, the tumor involved the phrenic nerve but not the brachial plexus. After adequate dissection and proximal and distal control of the involved veins, en bloc resection of the tumor and invaded structures was performed. Immediate revascularization between the left brachiocephalic vein and superior vena cava was accomplished by the interposition of a ringed polytetrafluoroethylene graft (12 mm). Because of the several previous surgical interventions in this area, the large skeletal defect, and the potential development of paradoxical movement, bony and soft tissue reconstruction and stabilization were achieved with Vicryl mesh (Ethicon, Somerville, NJ) and omental transposition, respectively.

Pathologic examination confirmed the initial diagnosis of radiation-induced sarcoma; all margins were free of tumor. The patient recovered without complications and was discharged on postoperative day 14.

Comment

Traditionally, radical surgical procedures for neurovascular disorders [5] and bronchogenic malignancies [6, 10] involving the thoracic outlet have been associated with high operative mortality and serious complications, such as fatal hemorrhage from the subclavian vein and artery or permanent neurologic damage to the extremity from T-1 or C-8 injury in the process of either dissecting the brachial plexus for tumor-free margins or removing the first rib. Although surgical experience with malignancies involving the thoracic outlet are limited to superior sulcus tumors [6], neoplastic involvement of the subclavian vessel and brachial plexus has long been considered a contraindication to any surgical approach because of the dismal outcome and high cost/benefit ratio.

Primary and metastatic nonbronchogenic tumors of the superior aperture of the thorax are uncommon lesions that encompass a kaleidoscopic panorama of benign and malignant bone and soft-tissue diseases, the peculiarities of which are their local aggressiveness, tendency to encapsulate the structures lying in this target area, high local recurrence rate, and, for some, propensity to metastasize [7, 8, 11]. Because of this, affected patients are highly symptomatic and may have shortened survival. The surgical management of these tumors should aim to relieve resulting thoracic outlet syndromes and minimize the risk of local recurrence through radical clearance of the tumor. Any surgical attempt is justifiable if the risks of operation are low and no other treatment option offers equivalent chance of cure.

Our results derive from a small and heterogeneous series, reflecting the rarity and variety of the disease. However, they provide evidence that primary and metastatic nonbronchogenic neoplasms of the thoracic outlet can be successfully managed by aggressive, wide, and radical surgical resection with low morbidity and mortality and encouraging long-term results. These objectives have been obtained using the described anterior transcranial approach.

Compared with other anterior [12], transaxillary [5], or

posterior [6] techniques, the transcervical approach offers several advantages: superb exposure of the entire thoracic outlet, safe dissection, and complete surgical clearance of the primary tumor mass-involved segments regardless of their anterior, middle, or posterior location. Moreover, it does not preclude complementary one-stage thoracotomy or sternotomy if resection of adjacent structures is necessary. The key to the success of this operation is the removal of the medial half of the clavicle. Resecting the clavicle and dividing its posterior periosteum and underlying subclavian muscle allows good control and deep dissection of adjacent subclavian vein, anterior scalenus muscle, phrenic nerve, and subclavian artery, and leaves no disability and minimal disfigurement. Using our transcervical approach, resection for wide, tumor-free margins of the primary lesion and involved outlet structures has never represented a major operative problem, and this is underlined by the fact that we failed to observe local tumor recurrence during follow-up. In contrast, 7 of 14 patients had an unsuccessful surgical attempt to remove the tumor before referral. This high local failure rate underscores the propensity of these tumors to recur locally and may in part be explained by the execution of a simple excision or a nonradical operation. In our opinion, to avoid the risk of tumor spread outside the affected area and to obtain a radical margin for superficial and deep-seated outlet neoplasms, the whole tumor-bearing compartment must be removed.

In the present series, the most common nonvascular outlet structures involved were the first rib (50%), anterior scalenus muscle (43%), and phrenic nerve (43%), and their resection was managed safely and effectively. Ten patients had compression or involvement of outlet vessels. Involvement of subclavian and internal jugular veins and related branches was managed by ligation after obtaining proximal and distal control because of the rich collateral circulations, without noticeable complications. Similarly, ligation of major branches of the subclavian artery, including the vertebral artery, was safely performed, provided no cerebrovascular disease was present.

In contrast, involvement of either brachiocephalic vein, the superior vena cava, and the subclavian artery often adds hazards to the operation. Two patients with a nonbronchogenic outlet neoplasm had partial invasion of the origin of the superior vena cava and the cephalic portion of the ipsilateral brachiocephalic vein. In this circumstance, clamping and prosthetic revascularization of the superior vena cava with the residual brachiocephalic vein were sufficient to maintain adequate blood flow in the graft to avoid extensive thrombosis and were not associated with intraoperative hemodynamic complications; these observations are in line with our previous experience [13]. It is equally important to avoid fatal ischemic complications of the upper limb, which have been reported [6, 10] when resection of the subclavian

artery is mandatory. In this situation, immediate revascularization either by end-to-end anastomosis, whenever technically feasible, or by vascular grafts is performed; we use externally supported polytetrafluoroethylene grafts because they tend to remain patent. Taken together, these observations should break down some of the barriers that have for so long affected the management of patients with subclavian involvement by the outlet tumor.

In summary, the proposed anterior transcervical approach may be curative not only for bronchogenic tumors extensively involving the thoracic inlet [9], but also for the infrequent and heterogeneous histologic types of non-bronchogenic tumors originating in any of the structures of this target area. To obtain wide and radical margins and thereby to keep the local recurrence rate low, the whole tumor-bearing compartment must be removed. Vascular invasion should no longer be regarded as a contraindication to surgical resection. Because of its related hazards and because many of these tumors involve vital adjacent structures, this transcervical approach should be performed by experienced surgeons representing the specialties of thoracic and vascular surgery and skin and soft tissue resection and reconstruction.

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Complement Inhibition With Soluble Complement Receptor Type 1 in Cardiopulmonary Bypass

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Although complement activation during cardiopulmonary bypass (CPB) is well documented, its pathogenic role in postperfusion organ injury is unproven. In this study, soluble human complement receptor type 1 (sCR1), a potent inhibitor of complement activation, was used to determine the contribution of complement activation to pulmonary injury in a porcine model of CPB. In vitro experiments demonstrated that sCR1 inhibits both classic and alternative complement pathways in the pig. Seven control piglets and 6 piglets treated with sCR1 (12 mg/kg intravenously) underwent 2 hours of hypothermic (28°C) CPB followed by 2 hours of observation. In control piglets, total hemolytic complement activity and functional activities of C3 and C5 declined to 61.3%, 67.8%, and 61.4% of prebypass values, respectively, after 2 hours of CPB. Plasma from animals treated with sCR1 had virtually no hemolytic activity (total hemolytic complement activity <5% of baseline), demonstrating effective complement inhibition. Similar degrees of neutro-

penia developed in the two groups during CPB, and there was no difference in post-CPB lung tissue myeloperoxidase level. Two hours after CPB, pulmonary vascular resistance increased 338% in control piglets but only 147% in piglets pretreated with sCR1 ($p < 0.05$); the alveolar-arterial gradient was not significantly different between controls (331 ± 52 mm Hg) and piglets receiving sCR1 (290 ± 85 mm Hg). Histologic examination revealed similar degrees of pulmonary edema in both groups. These data constitute direct evidence that complement activation plays a pathogenic role in lung injury after CPB. Although pretreatment with sCR1 ameliorated lung injury after CPB, resulting in decreased pulmonary hypertension, complement inhibition did not improve post-CPB oxygenation and had no significant effect on leukocyte kinetics or lung histology. Thus, complement participates in the pathogenesis of lung injury after CPB, but is not responsible for all of the pulmonary damage.

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In the United States each year, nearly 400,000 people are placed on cardiopulmonary bypass (CPB) [1]. Although CPB supports life-saving surgical procedures, significant morbidity and mortality attend its use. A large body of evidence suggests that a portion of the morbidity associated with CPB may be attributed to the generalized inflammatory response caused by extracorporeal circulation [2, 3]. This inflammatory response involves activation of the coagulation and kallikrein cascades, the fibrinolytic system, and the complement system. Much recent work has focused on the role of complement activation in postbypass organ injury [4, 5]. Although complement activation during CPB is well documented [6, 7], its pathogenic role in postperfusion organ injury is unproven. In this study, soluble human complement receptor type 1 (sCR1, designated BRL55730 by SmithKline Beecham), a potent inhibitor of complement activation, was used to determine the contribution of complement activation to pulmonary injury in a porcine model of CPB.

Material and Methods

Surgical Manipulations

Thirteen piglets weighing 8 to 10 kg were premedicated with ketamine (40 mg/kg intramuscularly) and anesthetized with pentobarbital sodium (Nembutal; Abbott Laboratories, North Chicago, IL; 30 mg/kg intravenously). A tracheostomy was performed, and the pigs were ventilated with 100% oxygen at a tidal volume of 15 mL/kg using a volume-cycled ventilator. Positive end-expiratory pressure was set at 5 cm H₂O. A polyethylene cannula was placed in the femoral artery for pressure monitoring, and a Swan-Ganz catheter was passed through the femoral vein. Additional doses of pentobarbital sodium (50 mg intravenously) were given every 30 to 60 minutes as required. After median sternotomy, a polyethylene cannula was placed in the left atrium for pressure monitoring and blood sampling. All animals received heparin (300 U/kg intravenously). sCR1, prepared as previously described [8], was provided by T Cell Sciences, Inc, Cambridge, MA. Treated animals ($n = 6$) received sCR1 (6 mg/kg intravenously) just before the initiation of CPB and again at the conclusion of 2 hours of CPB. Control

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animals ($n = 7$) received saline infusions. Cardiopulmonary bypass was initiated via cannulas placed in the right atrium and ascending aorta. A pulmonary artery vent was placed after initiation of bypass. The bypass circuit included a Sarns roller pump, a Bentley-10 Plus bubble oxygenator, and a 40- μ m in-line arterial filter. The prime consisted of 1,200 mL of a mixture of fresh homologous blood and crystalloid in a proportion calculated to produce a final hematocrit of 0.25. Animals were cooled to 28°C. Mean systemic arterial pressure was maintained at 50 to 55 mm Hg with pump flows of 80 mL/kg when temperature was greater than 32°C and 50 mL/kg when the temperature was less than 32°C. After aortic cross-clamping and cardioplegic arrest of the heart for 60 minutes, the animals were rewarmed. At the conclusion of 2 hours of CPB, an isoproterenol infusion ($0.1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) was started and the animals were weaned from bypass. The animals were stabilized over the next 30 minutes, isoproterenol administration was discontinued, and hemodynamic measurements were recorded for 2 hours after stabilization. At the conclusion of this period, fully anesthetized animals were sacrificed by intravenous injection of potassium chloride. Portions of the right lung were removed for assessment of myeloperoxidase content. The left lung was perfusion-fixed with 300 mL of 5% glutaraldehyde in 0.15 mol/L cacodylate buffer (pH = 7.2) through the pulmonary artery and sections were removed for histologic study.

An additional 4 piglets served as surgical controls. They underwent tracheostomy, placement of monitoring lines, sternotomy, and heparinization as described above. However, they were not placed on CPB. Two of these animals received sCR1 in two divided doses as described above. Hemodynamic measurements were recorded in these 4 animals for 4 hours after surgical preparation. At the conclusion of the 4 hours, five portions of lung were removed from each untreated animal for determination of baseline myeloperoxidase (MPO) activity (see below).

Physiologic Measurements

Arterial blood gases were measured after sternotomy, every 15 minutes during CPB, and at 30, 60, 90, and 120 minutes after discontinuing CPB. Ventilation was adjusted to maintain arterial carbon dioxide tension at 30 to 35 mm Hg. Hemodynamic measurements (heart rate, mean arterial pressure, pulmonary artery pressure, left atrial pressure, and thermoluted cardiac output) were obtained after sternotomy and at 30, 60, 90, and 120 minutes after CPB. Pulmonary vascular resistance (PVR) was calculated according to the formula $\text{PVR} = 79.92 \times (\text{mean pulmonary arterial pressure} - \text{mean left atrial pressure}) / \text{cardiac output (L/min)}$. During CPB, rectal and esophageal temperature, flow rate, and mean arterial pressure were monitored continuously.

Laboratory Studies

Arterial blood samples for determination of total hemolytic complement activity (CH_{50}), functional titers of the third and fifth components of complement (C3 and C5), complete blood counts, and plasma levels of sCR1 were drawn before sternotomy; after heparinization; 15, 30, 60,

and 90 minutes after beginning CPB; and 5, 30, 60, 90, and 120 minutes after cessation of CPB. To assess pulmonary sequestration of leukocytes, simultaneous left and right atrial blood samples were drawn 5, 30, 60, 90, and 120 minutes after weaning from CPB. Complete blood counts were performed by Coulter counter, and differential cell counts were done manually. Total hemolytic complement activity was determined by the method of Mayer [9]. The titers of C3 and C5 were determined in control animals by specific functional hemolytic assay [10, 11]. All complement titers are expressed as a percentage of poststernotomy value, and all are corrected for hemodilution using the formula: corrected titer = measured titer $\times$ (poststernotomy hematocrit/hematocrit at time of measurement). Plasma sCR1 levels were quantitated by a double polyclonal bead enzyme immunoassay using specific rabbit anti-sCR1 antibodies developed by T Cell Sciences, Inc. Myeloperoxidase activity in lung tissue was assessed using a standard spectrophotometric functional assay [12]. Myeloperoxidase activity is expressed in international MPO units per gram of tissue: one unit of enzyme activity is defined as the amount of MPO that produced an absorbance change of 1.0 per minute per milligram of tissue (wet weight) at 37°C.

Histologic Examination

Perfusion-fixed samples of lung tissue were processed for hematoxylin and eosin staining and histologic examination. Samples from each lobe of the right lung were examined by a pathologist who was blinded to the treatment received by each animal.

sCR1 Activity In Vitro

Varying concentrations of sCR1 were added to various dilutions of porcine serum and then incubated with antibody-sensitized sheep erythrocytes ($1 \times 10^8/\text{mL}$) for 1 hour at 37°C to assess inhibition of the classic pathway [9] or with unsensitized rabbit erythrocytes ($1 \times 10^8/\text{mL}$) for 1 hour at 37°C to assess inhibition of the alternative pathway [13]. In either case, the percent inhibition of complement activation was determined by comparing the percent erythrocyte lysis in the serum to which sCR1 had been added with the percent lysis in the serum to which buffer had been added.

Statistical Analysis

All values are expressed as mean $\pm$ standard error of the mean. Comparisons between groups were made using analysis of variance for repeated measures. Comparisons within groups were performed with Duncan's test for multiple comparisons. Myeloperoxidase activities were compared with Student's *t* test.

Animal Care

All animals received humane care in compliance with the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH publication No. 85-23, revised 1985).

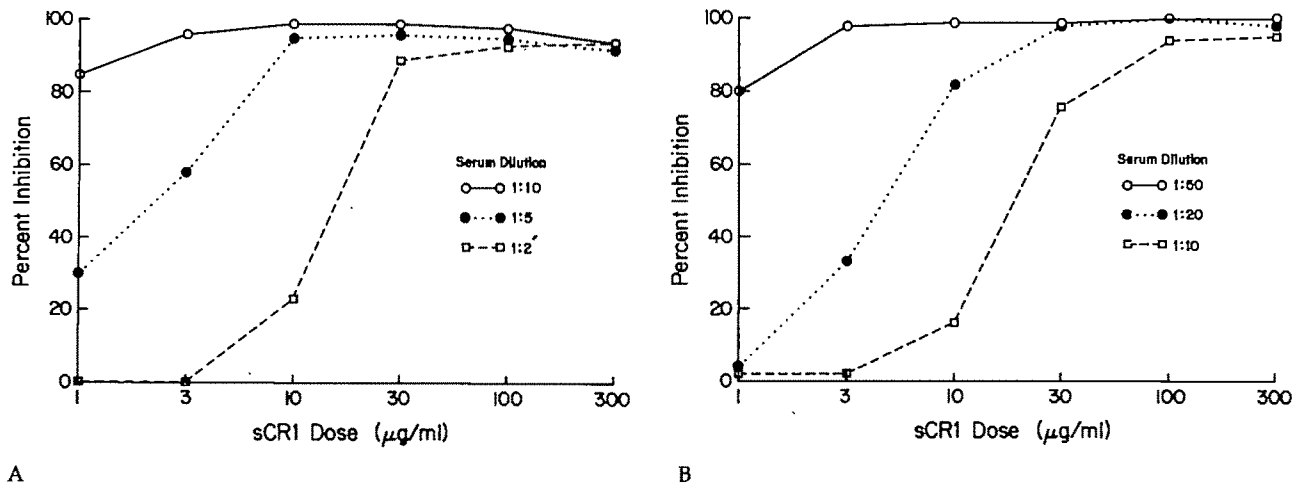


Fig 1. Soluble human complement receptor type 1 (sCR1) inhibition of classic and alternative pathways of complement activation in porcine serum *in vitro*. Percent inhibition of complement activation was determined by comparing percent erythrocyte lysis in serum to which sCR1 was added with percent lysis in serum to which buffer was added. Figure 1A shows inhibition of complement-mediated lysis of antibody-coated sheep erythrocytes (classic pathway) and Figure 1B demonstrates inhibition of complement-mediated lysis of rabbit erythrocytes (alternative pathway). Data are presented for three porcine serum dilutions, as indicated.

Results

Survival

All animals survived CPB and the 2-hour post-CPB observation period. One sCR1-treated animal was excluded from analysis because histologic examination of the lung revealed chronic pneumonia.

Inhibition of Complement Activation *In Vitro* by sCR1

Initial experiments were performed to determine whether human sCR1 was able to inhibit activation of the classic and alternative pathways of porcine complement. Human sCR1 inhibited the lysis of antibody-sensitized sheep erythrocytes (the classic pathway) by porcine serum at relatively low doses (Fig 1A). Similarly, human sCR1 effectively inhibited the lysis of unsensitized rabbit erythrocytes (the alternative pathway) by porcine serum (Fig 1B).

Inhibition of Complement Activation During Cardiopulmonary Bypass

Experiments were also performed to determine whether there was activation of the complement system during CPB in pigs and whether human sCR1 was capable of inhibiting that activation. There was ongoing consumption of complement during the 2 hours of CPB (Fig 2). At the final measurement, 2 hours after CPB, CH₅₀, C3, and C5 levels had declined to 61.3% ± 5.2%, 67.8% ± 8.9%, and 61.4% ± 8.4% of prebypass values, respectively. The levels of CH₅₀, C3, and C5 during and after bypass were significantly different from baseline at all measured time points ($p < 0.05$). In Figure 3, CH₅₀ values and plasma sCR1 levels are plotted for animals treated with sCR1. Plasma from these animals had virtually no hemolytic activity; the CH₅₀ value was less than 5% of baseline at all time points after sCR1 administration, indicating effective complement inhibition. The two doses of sCR1 administered during the experiment resulted in plasma sCR1 levels greater than 50 μg/mL at all time points.

Neutrophil Counts and Lung Tissue Myeloperoxidase

Neutrophil counts were similar in both groups over the entire course of the experiment (Fig 4). Significant neutropenia developed in all piglets during CPB. Neutrophil counts in control animals fell from the poststernotomy value of 5,002 ± 1,443 cells/μL to 768 ± 280 cells/μL at 90 minutes of CPB. Neutrophil counts in treated animals fell from 8,285 ± 3,134 cells/μL to 916 ± 159 cells/μL over the same period. After CPB, there was a gradual increase in neutrophil counts in both groups. Although right atrium to left atrium neutrophil gradients 5 minutes after reestablishment of pulmonary blood flow were greater in treated animals (446.2 ± 265.2 cells/μL) than in controls (175.7 ± 113.6 cells/μL) these differences were not significant ($p = 0.34$).

The mean lung tissue MPO level in animals that served

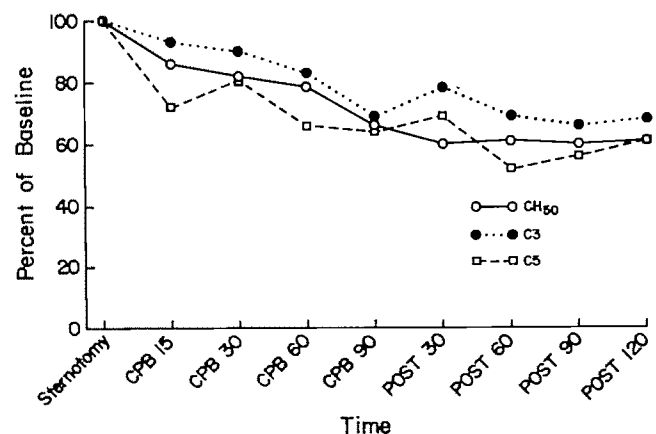


Fig 2. Total hemolytic complement activity (CH₅₀), C3, and C5 titers during cardiopulmonary bypass in control piglets. Data are expressed as percentage of poststernotomy values. All data are corrected for hemodilution. (CPB 15, 30, 60, and 90 refer to time points during cardiopulmonary bypass, and Post 30, 60, 90, and 120 refer to time points after cardiopulmonary bypass.)

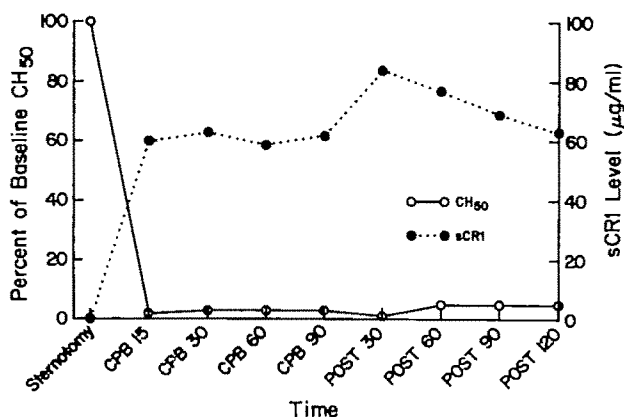


Fig 3. Total hemolytic complement activity (CH_{50}) and plasma soluble human complement receptor type 1 (sCR1) levels during cardiopulmonary bypass in treated piglets. CH_{50} data are expressed as percentage of poststernotomy value and are corrected for hemodilution. sCR1 doses (6 mg/kg intravenously) were given after sternotomy and at the conclusion of 2 hours of cardiopulmonary bypass. (Sternotomy refers to after sternotomy; CPB 15, 30, 60, and 90 refer to time points during cardiopulmonary bypass, and Post 30, 60, 90, and 120 refer to time points after cardiopulmonary bypass.)

as surgical controls (sternotomy without CPB) was 0.055 ± 0.005 units/g. Postbypass lung tissue MPO levels were 0.211 ± 0.132 units/g in sCR1-treated animals and 0.217 ± 0.208 units/g in untreated animals. Although CPB caused an increase in lung tissue MPO level in both groups as compared with surgical controls, MPO levels were not significantly different between treated and untreated animals after CPB ($p = 0.98$).

Pulmonary Function

Pulmonary vascular resistance increased significantly in both groups after CPB (Fig 5). However, PVR at all points after CPB was significantly lower in treated than in untreated animals ($p < 0.05$). At 2 hours after bypass, PVR in control and sCR1-treated animals was $2,947 \pm 304$ and $1,725 \pm 311$ dynes $\cdot$ sec $\cdot$ cm $^{-5}$, respectively ($p < 0.05$).

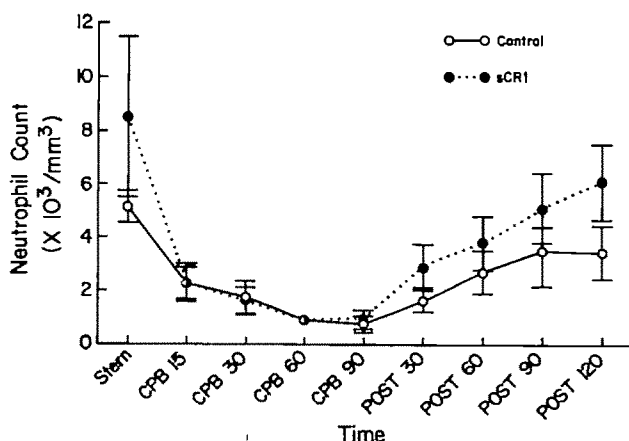


Fig 4. Neutrophil counts during cardiopulmonary bypass in control and treated piglets. (CPB 15, 30, 60, and 90 refer to time points during cardiopulmonary bypass, and Post 30, 60, 90, and 120 refer to time points after cardiopulmonary bypass; sCR1 = soluble human complement receptor type 1.)

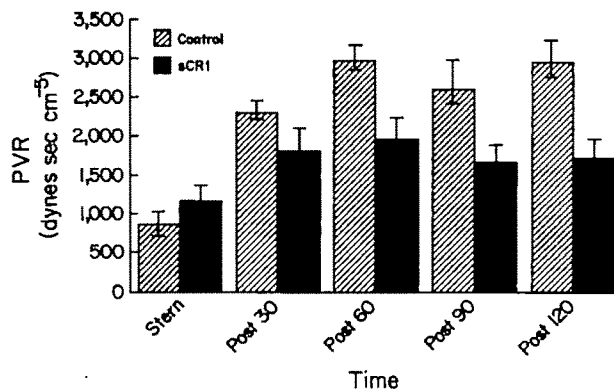


Fig 5. Pulmonary vascular resistance (PVR) in control and treated piglets. Poststernotomy (stern) (baseline) and postbypass (Post) values are displayed. ($p < 0.05$ for soluble human complement receptor type 1 [sCR1]-treated versus control animals by analysis of variance for repeated measures.)

There were no differences in left atrial pressure (2 to 4 mm Hg) or cardiac output (600 to 900 mL/min) between groups after CPB. Alveolar-arterial gradients for oxygen also increased significantly in all animals after 2 hours of CPB, but there was no significant difference between control and treated groups (Fig 6).

During the 4-hour observation period after sternotomy, there was no change in hemodynamic parameters or pulmonary function in any of the 4 piglets that served as surgical controls. Administration of sCR1 to 2 of these piglets had no effect on systemic or pulmonary hemodynamics or oxygenation.

Histology

Control and sCR1-treated animals had similar pulmonary histology after CPB. There were multifocal areas of pulmonary edema and neutrophil sequestration surrounded by areas of normal lung in both treated and untreated animals. Ten to 20% of each lung field had evidence of pulmonary edema.

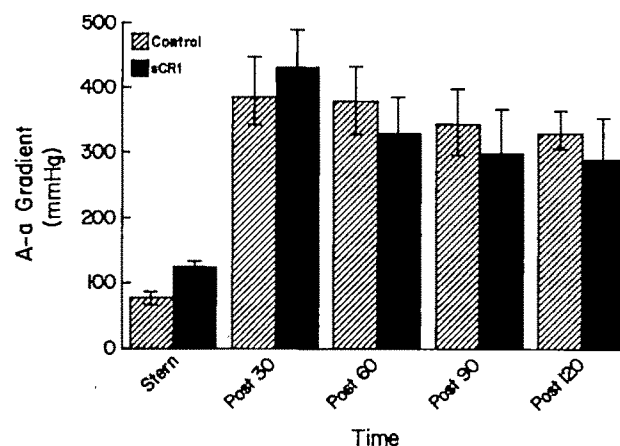


Fig 6. Alveolar-arterial (A-a) gradients for oxygen in control and treated piglets. Poststernotomy (Stern) (baseline) and postbypass (post) values are displayed. ($p =$ not significant for soluble human complement receptor type 1 [sCR1]-treated versus control animals.)

Comment

Kirklin [2] and others [3, 4] have hypothesized that much of the pulmonary damage associated with CPB is caused by a generalized inflammatory reaction that occurs when blood is exposed to synthetic surfaces of the bypass circuit. Extracorporeal circulation causes rapid and extensive complement activation in humans [4-7]. It is generally accepted that complement is activated predominantly by the alternative pathway early in CPB and that the protamine-heparin complex causes further activation via the classic pathway [14]. Because complement activation can cause increased vascular permeability, vasoconstriction, and leukocyte chemotaxis and activation [15, 16], and each of these phenomena occurs during CPB, it has been suggested that complement activation may be responsible for the pulmonary damage seen after CPB [2-4]. Kirklin and associates [17] found that complement levels 3 hours after CPB correlate with cardiac, pulmonary, and renal dysfunction. Moore and colleagues [18] reported that extensive complement activation is associated with prolonged postoperative ventilatory support. Taken together, these studies suggest that complement activation is associated with postperfusion pulmonary dysfunction, but they do not prove that it is responsible for the injury.

Previous attempts to modulate complement activation during human CPB have included use of membrane oxygenators, steroids, and heparin-coated bypass circuits. Although membrane oxygenators have advantages over bubble oxygenators, there is no consensus that they cause less complement activation during CPB. Rather, complement activation varies with individual proprietary oxygenators, some models causing less activation than others [19, 20]. Recently, heparin-coated bypass circuits have been shown to reduce complement activation during CPB; however, they do not completely eliminate complement activation, and no physiologic benefit has been reported with use of such equipment [21]. Although steroid therapy has been associated with a moderate decrease in complement activation in some studies [22], others have found no significant effect [23].

Experimental studies have also attempted to define the role of complement activation in postperfusion organ injury. Cobra venom factor therapy causes depletion of complement; it reduced pulmonary dysfunction in sheep placed on venovenous bypass [24]. However, cobra venom factor depletes complement by causing its activation and consumption; this mechanism of action may itself cause organ damage, making results of studies employing cobra venom factor difficult to interpret. Finally, FUT-175, a nonspecific protease inhibitor, has been shown to decrease complement activation in a model CPB circuit [23], but it has not been used in an animal model of CPB. Thus, none of these attempts to decrease complement activation has provided conclusive evidence that complement activation is pathogenic in CPB.

Until now there has been no practical pharmacologic means to reduce complement activation during CPB. sCR1 is a recombinant form of human complement receptor type 1 that lacks the membrane-bound and cytoplasmic domains of the native molecule [8]. Human comple-

ment receptor type 1, which is present on normal erythrocytes, neutrophils, and other blood cells, protects these cells from bystander damage when they are present at inflammatory foci. The method of protection is believed to be inactivation of the C3 and C5 convertases [8]. sCR1 has similar biologic activity. It binds to C3b and C4b, causing degradation and inactivation of the C3 and C5 convertases of the classic and alternative pathways. It is effective *in vitro* against complement from human and rats [8]. sCR1 administration has reduced infarction size in a rat model of myocardial ischemia [8] and has been shown to delay hyperacute rejection of rat cardiac allografts in presensitized recipients [25]. Treatment with sCR1 also reduced pulmonary vascular injury in models of immune complex-induced alveolitis and cutaneous thermal injury [26]. In this study, we have used sCR1 to examine the role of complement activation in pulmonary injury produced by CPB.

Pulmonary dysfunction remains a significant problem after CPB [4, 5, 27]. The piglet is an appropriate animal for study of pulmonary injury after CPB because pigs tolerate CPB poorly, demonstrating marked stigmata of postperfusion organ injury. During CPB, increased microvascular permeability and pulmonary dysfunction develop in pigs [28]. Kirklin [2] has shown that pigs placed on CPB experience complement activation. Others have demonstrated that injection of complement-activated plasma causes hypoxemia, pulmonary hypertension, pulmonary edema, and pulmonary leukostasis in pigs [29]. In our model, CPB produced lung injury manifest as increased alveolar-arterial gradient for oxygen, increased PVR, and histologic alveolar injury. There was associated consumption of complement during CPB, with CH₅₀, C3, and C5 levels falling to approximately 60% of baseline; this is analogous to the situation in human CPB [23].

Preliminary *in vitro* studies confirmed that sCR1 effectively inhibits complement activation in pig plasma. At microgram per milliliter concentration, sCR1 inhibited both classic and alternative pathways *in vitro*. Because specific antibodies to products of porcine complement activation (C3a, C5a) are not commercially available, we were unable to perform direct measurements of complement activation during CPB. However, plasma from animals pretreated with sCR1 had virtually no hemolytic activity; this strongly supports significant inhibition of complement activation.

In this model, treatment with sCR1 significantly reduced pulmonary hypertension after CPB. The mechanism for this decrease in PVR is unclear. In preliminary experiments, sCR1 administration to animals after sternotomy without CPB resulted in no change in hemodynamics or pulmonary function. This suggests that sCR1 is not a direct pulmonary vasodilator. Treatment with sCR1 did not significantly affect post-CPB alveolar-arterial gradient, pulmonary histology, lung tissue myeloperoxidase, or leukocyte kinetics. Thus, complement inhibition reduced but did not eliminate post-CPB pulmonary dysfunction.

This result is not surprising. Cardiopulmonary bypass causes a diffuse inflammatory reaction characterized by activation of multiple humoral amplification cascades.

While CPB results in complement activation, it also causes kinin generation, consumption of coagulation factors, fibrinolysis, liberation of thromboxane A₂, and activation of platelets and neutrophils [2, 3]. Activation of the kinin system alone can result in neutrophil activation, increased vascular permeability, and vasoconstriction [2]. Neutrophils can cause tissue damage by generation of reactive oxygen species, liberation of proteases, and release of products of the arachidonic acid cascade [2, 3]. We have previously demonstrated that neutrophil depletion, like complement inhibition, reduces but does not eliminate the pulmonary injury associated with CPB [30]. This suggests that therapies targeted to only one arm of the complex inflammatory cascade initiated by CPB will not eliminate postperfusion organ injury.

In this study, we used sCR1, a potent inhibitor of complement activation, to demonstrate that complement activation participates in the pathogenesis of lung injury after CPB. However, complement activation does not account for all of the pulmonary damage in this porcine model. More effective reduction of CPB-associated organ injury will probably require modulation of other arms of the inflammatory cascade initiated by CPB or inhibition of the final common pathways of inflammation.

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Cardiopulmonary Bypass and Cellular Immunity: Changes in Lymphocyte Subsets and Natural Killer Cell Activity

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To investigate whether cell-mediated immunity responses are suppressed or activated by the effect of cardiopulmonary bypass (CPB), we studied peripheral blood lymphocyte subsets and antibody-dependent cell-mediated cytotoxicity in 52 adult patients who had undergone open heart operations. Lymphocyte function also was studied with regard to mixed lymphocyte reaction, which indicates the amount of DNA synthesis of lymphocytes, and natural killer (NK) cytotoxicity, which represents the killing activity of NK cells on the tumor cells (K-562), in 11 patients. The total T lymphocyte (OKT3+ and OKT11+) number showed no significant change during CPB. Suppressor/cytotoxic T cell (OKT8+)

and NK cell (Leu7+ and Leu11+) numbers were found to be remarkably increased. However, helper/inducer T cell (OKT4+) and B cell (Leu12+) numbers were decreased during CPB. Antibody-dependent cell-mediated cytotoxicity was elevated during CPB. All of these changes were almost returned to the preoperative levels by the seventh day after operation. Mixed lymphocyte reaction and NK cytotoxicity were also activated during CPB. The results show that heart operations in which cardiopulmonary bypass is used are associated with activation of cytotoxic cell-mediated immunity.

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Because cardiopulmonary bypass (CPB) used in open heart operations is a nonphysiological assisting device, it has been considered to cause specific changes in immunity and lead to development of postoperative infections. The possibilities of graft-versus-host diseases developing after open heart operation are relatively high. Taking account of these findings, the specificity of immunological changes in cardiac operations, including changes in mitogenic responsiveness, is now the subject of investigation. Furthermore, understanding the alterations in lymphocyte functions in open heart operations is important as a control study for immunological monitoring of rejection in heart transplantation. In this report, we examined the effect of cardiac operation on cell-mediated immunity by comparing the changes in each lymphocyte subset. Because natural killer (NK) cells showed a very interesting change, we performed further investigations of mixed lymphocyte reaction (MLR) and NK cytotoxicity to define the significance of the changes in this nonspecific immunity during CPB.

Material and Methods

Lymphocyte Subsets and Antibody-Dependent Cell-Mediated Cytotoxicity

We studied 52 adult patients, 35 men and 17 women, who underwent open heart operation at the National Cardiovascular Center. Mean age of the patients was 54.6 ± 12.9 (standard deviation). Twenty-three patients had valvular disease, 25 had ischemic heart disease, and 4 had other diseases. Mean CPB time was 160.2 ± 50.0 minutes, and the following oxygenators were used: bubble: Bard H-1700, 10 patients; polyethylene membrane: Bard HF4000, 10 patients; polypropylene membrane: Travenol LPM50, 10 patients; Cobe IF-CML, 11 patients; and silicone membrane: MERA HSO-2.5, 11 patients.

ANALYSIS OF LYMPHOCYTE SUBSETS. Changes in peripheral blood lymphocyte subsets were measured by flow cytometric analysis using monoclonal antibodies as follows: OKT3(CD3), OKT4(CD4), OKT8(CD8), and OKT11(CD2) from Ortho Diagnostics Inc; and Leu7(K cell and NK cell subsets), Leu11(CD16), and Leu12(CD19) from Becton Dickinson Inc.

Blood samples were taken preoperatively (before anesthetizing), when the CPB was turned on, when it was turned off, and on the first, second, fifth, and seventh postoperative days. Measurements were calculated by multiplying the number of lymphocytes times the ratio of each subset, and then correcting for the influence of blood

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dilution with the hematocrit value. No steroids were used while the CPB was on and after operation, but 100 mg/L of betamethasone was contained in the cardioplegic solution.

ANTIBODY-DEPENDENT CELL-MEDIATED CYTOTOXICITY. Peripheral blood lymphocytes (200 counts/0.1 mL) and MOLT cells (target cells: 200 counts/0.1 mL) were mixed in Falcon plastic tube and incubated in 5% carbon dioxide for 6 hours at 37°C. After that all cells secreting immunoglobulin were measured by plaque assay using protein A (Pharmacia Fine Chemicals, Uppsala, Sweden) coupled sheep red cells. Antibody-dependent cell-mediated cytotoxicity is presented as a percentage: (plaque forming cells/total lymphocytes) $\times$ 100%.

Lymphocyte Function

To understand the changes in lymphocyte function during CPB, we examined MLR and NK activity. Lymphocytes were obtained from 11 adult patients (7 men and 4 women) who underwent open heart operation. The average age was 52.9 ± 10.0 years. Two patients had ischemic heart disease, and 9 patients had valvular disease. Oxygenators used were Maxima (7 patients), BOS-10 (3 patients), and HF4000 (1 patient).

MIXED LYMPHOCYTE REACTION. Lymphocytes were separated from peripheral blood samples, and only viable ones were counted. These lymphocytes were suspended in RPMI 1640 medium containing 10% fetal calf serum and adjusted to a concentration of $1 \times 10^5/0.1$ mL per well. The number of wells was 96 per microplate (Corning Co). Peripheral blood lymphocytes of 10 normal adult donors were treated with 20 Gy radiation. An equal volume of this lymphocyte suspension was added to each well as a stimulator. The lymphocytes were incubated in 5% carbon dioxide for 7 days at 37°C. These lymphocytes were then labeled with 1 μ Ci of tritium thymidine per well, incubated for an additional 16 hours, and harvested. As an index of the amount of DNA synthesis, the uptake of tritium thymidine was measured in a liquid scintillation counter. The result is presented as stimulation index: = allogenic lymphocyte activity (counts/min)/autologous lymphocyte activity (counts/min).

NATURAL KILLER CELL ACTIVITY. Lymphocytes separated from peripheral blood samples (effector cells) and K-562 cells labeled with chromium 51 (target cells) were mixed in RPMI 1640 medium containing 10% fetal calf serum with effector/target ratios of 60:1, 30:1, and 15:1, and incubated in 5% carbon dioxide for 6 hours at 37°C. After incubation, NK cytotoxicity was calculated from the radioactivity of chromium 51 in the supernatant and is presented as percent lysis = (experimental release - spontaneous release)/(maximum release - spontaneous release) $\times$ 100%. (Maximum release is total radioactivity in target cells.)

Results are presented as the mean $\pm$ the standard deviation, and the significance of the differences between the mean values was analyzed by paired two-tailed Stu-

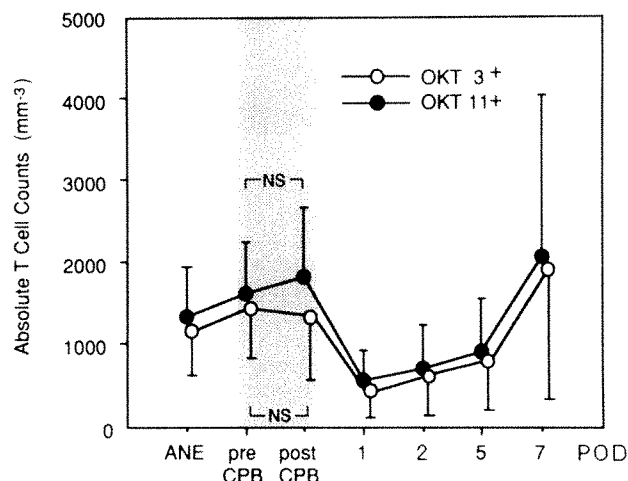


Fig 1. Absolute levels of circulating OKT3+ cells and OKT11+ cells after cardiac operation (mean $\pm$ standard deviation of the mean). No significant differences were found between before and after cardiopulmonary bypass. (ANE = induction of anesthesia; CPB = cardiopulmonary bypass; NS = not significant; POD = postoperative day.)

dent's *t* test for lymphocyte subsets and antibody-dependent cell-mediated cytotoxicity and Wilcoxon signed-ranks test for MLR and NK activity using the StatView program on a Macintosh Computer SE (Apple Computer Inc). A *p* value of less than 0.05 was considered significant.

All the patients were given detailed information on the design and aim of the study and then gave their consent to participate.

Results

Lymphocyte Subsets

OKT3+ AND OKT11+ CELLS. The number of OKT3+ cells, which indicates the total number of lymphocytes, and the number of OKT11+ cells, which indicates the number of E rosette formation T lymphocytes, were $1,431 \pm 589$ and $1,615 \pm 614/\mu$ L before CPB, respectively, but decreased prominently to 417 ± 301 and $555 \pm 369/\mu$ L, respectively, on the first postoperative day. These numbers, however, rose gradually after the first day and recovered to the preoperative levels on the seventh day after operation. The changes in the numbers of OKT3+ and OKT11+ cells during CPB were not significant (Fig 1).

OKT4+ AND OKT8+ CELLS. The number of OKT4+ cells, which indicates helper/inducer T cells, started decreasing during CPB ($p < 0.01$) and reached the lowest level on the first day after operation. In contrast, the number of OKT8+ cells, which indicates suppressor/cytotoxic T cells, increased during CPB ($p < 0.01$), but on the first postoperative day dropped to the lowest level. Both of them recovered to the preoperative levels or higher after a week (Fig 2).

Leu7+ AND Leu11+ CELLS. The numbers of Leu7+ and Leu11+ cells, which indicate NK cells, were 336 ± 260 and

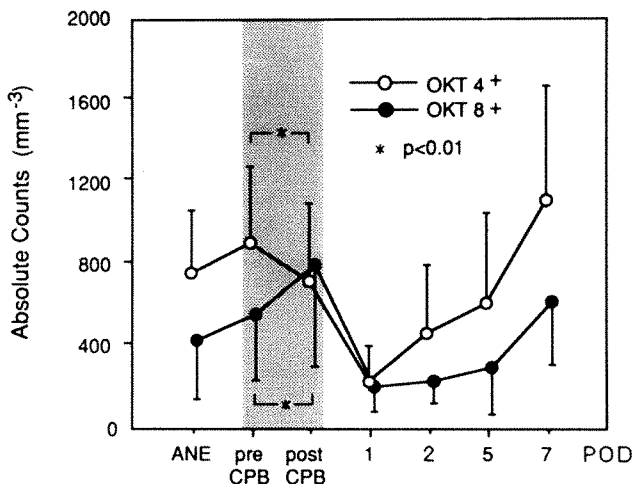


Fig 2. Absolute levels of circulating OKT4+ cells and OKT8+ cells after cardiac operation. The number of OKT4+ cells was decreased during cardiopulmonary bypass. (Abbreviations are as in Figure 1.)

398 ± 251/μL, respectively, before operation, and both of them increased remarkably during CPB to 389 ± 272 and 738 ± 446/μL, respectively ($p < 0.01$). The ratio of Leu7+ and Leu11+ cells to total lymphocytes also rose prominently from 13.2% ± 9.8% to 19.2% ± 12.8% in the case of Leu7+ and from 20.3% ± 11.3% to 33.1% ± 15.8% in the case of Leu11+. This result shows the real possibility of activation in nonspecific immunity during CPB. The numbers of Leu7+ and Leu11+ cells, however, decreased on the first postoperative day and kept decreasing until the seventh day (Fig 3).

Leu12+ CELLS. The level of Leu12+ cells, which corresponds to that of B cells, reduced during CPB significantly ($p < 0.0001$), and it took a week for the Leu12+ cell level to recover (Fig 4). However, every patient showed differ-

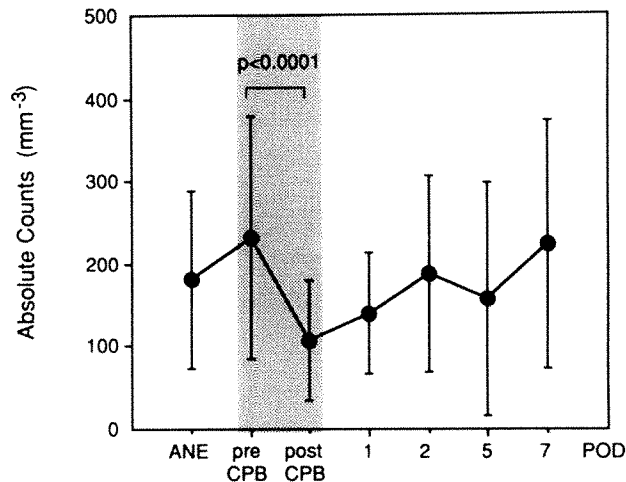


Fig 4. Absolute levels of circulating Leu12+ cells after cardiac operation. The number of Leu12+ cells was significantly reduced during cardiopulmonary bypass. (Abbreviations are as in Figure 1.)

ent degrees of change after operation, making it impossible to delineate a tendency in the change of Leu12+ cells in the postoperative period.

CARDIOPULMONARY BYPASS TIME AND NATURAL KILLER CELLS. The degree of change in lymphocyte subsets during CPB varies with the kinds of oxygenators used [1]. In particular, the change in NK cells was remarkable when the HF4000 oxygenator (Bard) and the MERA silicone membrane oxygenator were used. Thus we chose 20 patients in whom these two oxygenators were used and searched for the correlation between CPB time and an increase in Leu11+ cells during CPB. There was linear regression ($r = 0.936$; $p < 0.01$) on 7 selected data points, which was obtained using the StatView program of Macintosh computer SE (Apple Computer Inc) between them up to 150 minutes of CPB time in a scatterplot that clearly shows no linear correlation at all if all data points were included (Fig 5).

ANTIBODY-DEPENDENT CELL-MEDIATED CYTOTOXICITY. Antibody-dependent cell-mediated cytotoxicity activity, which represents the magnitude of K cell cytotoxicity, increased during CPB from 4.37% ± 1.94% to 5.61% ± 2.45% ($p < 0.0003$), but diminished on the first postoperative day and returned to the preoperative level by the seventh day after operation (Fig 6).

Mixed Lymphocyte Reaction and Natural Killer Cell Activity

The stimulation index calculated from MLR was 2.02 ± 0.92 before CPB and increased to 3.26 ± 1.99 after CPB ($p < 0.05$). Natural killer activity also rose significantly from 22.95% ± 12.2% to 27.99% ± 12.27% in the 30:1 culture ($p < 0.02$) (Fig 7). These results indicate a proliferation of blastogenesis and the activation of NK cells during CPB. However, the MLR started decreasing on the first post-

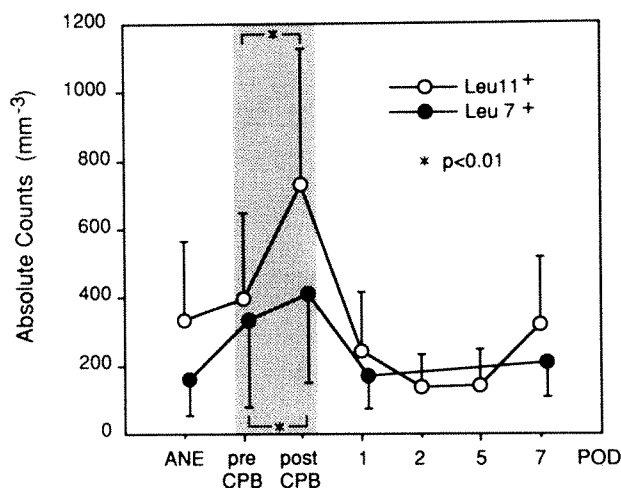


Fig 3. Absolute levels of circulating Leu11+ cells and Leu7+ cells after cardiac operation. Both of them were significantly increased during cardiopulmonary bypass. (Abbreviations are as in Figure 1.)

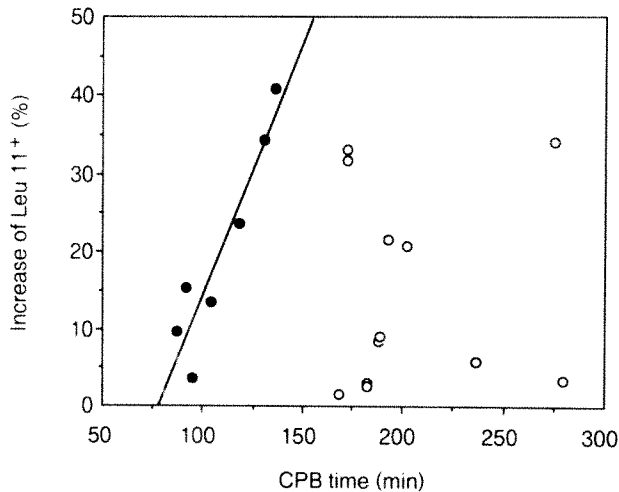


Fig 5. Relationship between cardiopulmonary bypass (CPB) time and the increase in Leu11+ cells during cardiopulmonary bypass. There was a significant correlation ($y = -50.5 + 0.65x$; $r = 0.936$; $p < 0.01$) between them up to 150 minutes (solid circles). However, if the data points at greater than 150 minutes (open circles) are included, this correlation becomes inconsistent.

operative day, whereas NK activity kept increasing until the seventh day after operation.

Comment

It has been reported that the body's ability to protect itself against infection is reduced during CPB in open heart operations due to a reduction in immunoglobulin and complement caused by blood dilution, physical cell destruction, and protein degeneration [2]. In this regard membrane oxygenators are considered more advanta-

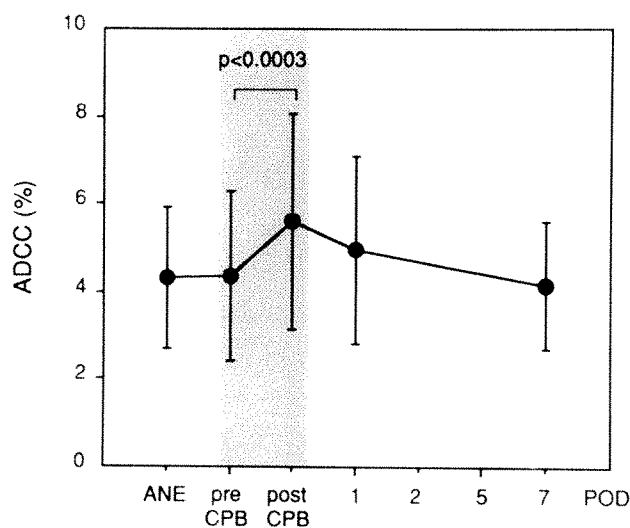


Fig 6. Changes in antibody-dependent cell-mediated cytotoxicity (ADCC) activity after cardiopulmonary operation. The ADCC activity was significantly increased during cardiopulmonary bypass. (Abbreviations are as in Figure 1.)

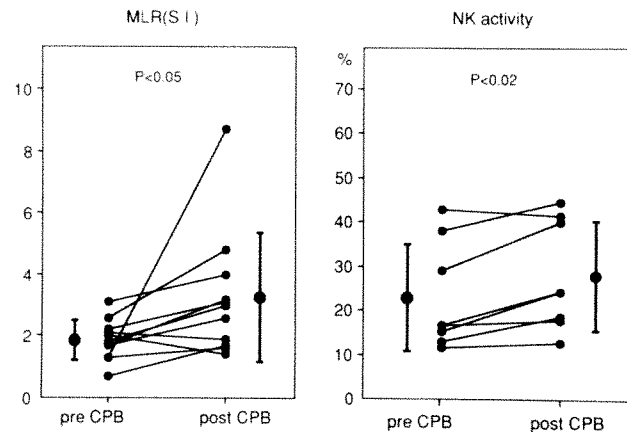


Fig 7. Changes in stimulation index (SI) of mixed lymphocyte reaction (MLR) and natural killer (NK) activity in 30:1 culture during cardiopulmonary bypass (CPB). Both of them were increased significantly.

geous than bubble oxygenators [3]. One of the major reasons for the complement reduction is its own consumption, caused by the increase in activity induced by the interaction between blood and foreign materials such as those used in oxygenators [4, 5]. The physical and chemical influence of CPB cannot be ignored, but the movement of complement mentioned above suggests to us the importance of the immunological reaction as an effect of CPB on the immune system. This immunological reaction can be seen in cell-mediated immunity as well as in humoral immunity. Because the degree of complement activation during CPB varies with which oxygenators are used [6], the immunological reaction is also presumed to occur in the oxygenators in the case of cell-mediated immunity. The immunological reaction caused by blood-artificial membrane interactions has already been studied in the field of dialysis, and the finding of promotion of interleukin-1 production indicates the activation of parts of cell-mediated immunity [7, 8]. Similar reaction to that in dialysis can be expected in membrane oxygenators.

The change in lymphocytes should be examined by their numbers and also their functions. Many studies have demonstrated that immunity is impaired in extracorporeal circulation using CPB as far as the number of lymphocytes is concerned. Roth and associates [9] reported a reduction in the total number of T cells. According to Ide and associates [10], the total number of T lymphocytes and B lymphocytes was markedly reduced during CPB, and this reduction in total T lymphocytes resulted from the reduction of helper/inducer T cells. Furthermore, Hisatomi and associates [11] reported that the number of OKT3+, OKT4+, and OKT8+ cells decreased significantly on the first or third postoperative day. In their studies, however, the number of total T lymphocytes was obtained without considering blood dilution during CPB, and each subset was compared by the composition of population to total lymphocytes, not by the absolute number. On the other hand, a reduction in the ratio of helper T cells to cytotoxic/suppressor T cells

was observed during CPB by Navarro and associates [12], and an increase in cytotoxic/suppressor T cells was suggested to contribute to the reduction in the ratio of helper T cells to cytotoxic/suppressor T cells. These findings are in agreement with our present report.

In examining immunity in open heart operations using CPB, the issue of blood dilution is always a matter of consideration. When investigating the change in immunity of an individual patient, the effect of blood dilution is one of the variables and does not need to be corrected for, but, as in our present study, it should be corrected for when the effect of oxygenators is examined. Total number of T and B lymphocytes decreased during CPB and remained decreased for a week after operation, as shown in other reports [9, 11]. Among lymphocyte subsets that we examined, the change in helper/inducer T cells was similar to that in total T lymphocytes and showed the lowest level on the first postoperative day. Because blood is diluted immediately after operation, the level of T cells, especially the helper/inducer T cell level of each patient, was quite low. Destruction and consumption of lymphocytes themselves during CPB and loss of ability to react against monoclonal antibodies due to the physical destruction of surface markers are also presumed to be responsible for this T cell level reduction. Under such conditions, however, the level of suppressor/cytotoxic T cells showed a clear increase during CPB. The number of NK cells also increased during CPB. This increase was so obvious that we noticed it before correcting for the effect of blood dilution.

We did not perform further individual examinations of suppressor T cells and cytotoxic T cells. However, if the change in suppressor T cells and cytotoxic T cells is responsible for the increase in OKT8+ cells during CPB, it is possible to say that the absolute number of lymphocytes with cytotoxicity increases during CPB. Although the mechanism of such a quantitative change has not been defined yet, Ide and associates [10] suggested T cell redistribution between bone marrow and peripheral blood as a mechanism of quantitative change in helper/inducer T cells during CPB. In the case of NK cells, suppressor T cells, and cytotoxic T cells, T cell distribution between peripheral blood and lymphoid tissue is also presumed to be a mechanism of their quantitative change. We took into consideration the effect of blood transfusion during CPB on changes in immunity. In our study, the number of both Leu11+ and OKT8+ cells increased during CPB in a nontransfusion group. There was no significant difference between changes in the transfusion group and the nontransfusion group.

In parallel with the examination of quantitative changes, MLR and NK activity were measured to determine their influence on each lymphocyte function. Both MLR and NK activity showed an increase during CPB. Natural killer activity particularly showed an increase on the first operative day. Furthermore, antibody-dependent cell-mediated cytotoxicity activity, which indicates cytotoxicity of monocytes or K cells, increased clearly during CPB. These tests, however, were performed using only

viable lymphocytes selected from samples. Therefore these findings do not immediately lead to the augmentation of lymphocyte function in each patient. Depressed lymphocyte blastogenesis has been reported during the early postoperative period [9, 13, 14]. Ryh nen and associates [15] reported that NK cell activity decreased on the second day after an open heart operation. Those studies, however, show the changes after the first postoperative day. In our study we observed the MLR increase as mentioned above, but it occurred immediately after operation, and on the first postoperative day it decreased as in the previous reports. On the other hand, Haeffner-Cavaillon and associates [16] suggested that CPB causes an increase in interleukin-1 activity in monocytes. Their report indirectly supports our findings, which demonstrate the activation of relatively primary cytotoxic immunity. Omokawa and associates [17] noted that blood-material interactions in dialysis enhance the interleukin-1 activity after 30 minutes up until 3 hours after extracorporeal circulation is started and that the enhancement is prominent when polyethylene is used as a dialyzer. Because polyethylene or polypropylene is commonly used for membrane oxygenators, a similar reaction may be expected. According to Ryh nen and associates [18], the number of antibody secreting cells (mostly B cells) and OKIa+ cells (activated T cells) in peripheral blood showed a tendency to increase after a cardiac operation, which indicates the possibility for part of the cell-mediated immunity to be activated during CPB.

We cannot determine if the cell-mediated immunity in each patient is activated or suppressed overall during CPB. The number of T cells decreases, but the viability of each cell is different. In this study CPB showed the possibility of activating cytotoxic cell-mediated immunity. Natural killer cells especially increased in number and function during CPB. This fact enables us to presume there is an increase in cytotoxicity in each patient.

Like a dialyzer during dialysis [17], the oxygenator, which is the largest contact area for blood and artificial material, is presumed to be the most likely place for immunity activation. However, if the operation is protracted, blood-material interactions may occur in the other contact areas such as cardiopulmonary bypass tubes and pumps. There is a report that shows an increase in activated suppressor/cytotoxic T cells after artificial heart implantation [19]. T nnesen and associates [20] suggested in their case report that transient augmentation of NK cell activity during CPB is related to the increasing level of blood adrenaline; however, NK cell activity decreased after operation because of an increased plasma cortisol level due to prolonged adrenaline infusion.

In our study there was a positive correlation coefficient between the number of NK cells and CPB time within a certain duration (within 150 minutes), but after 150 minutes of CPB the number of NK cells did not always increase. Although we failed to prove a direct linkage, the result implied that extended CPB might cause suppressed immunity, which could be due to saturation or damage of the epitopes or secondary hormonal effect.

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Relation Between Choice of Prostheses and Late Outcome in Double-Valve Replacement

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The purpose of this study was to determine if the combination of a mechanical and bioprosthetic valve in the aortic and mitral positions influences late morbidity and mortality when compared with patients who had dual mechanical or dual bioprosthetic valves inserted. We reviewed the course of 89 hospital survivors of combined aortic and mitral valve replacement. The mean postoperative follow-up interval was 6.6 years, with a total follow-up of 583 years (98% complete). At 12 months after operation, mean functional class decreased from 3.1 to 1.7 ($p < 0.05$) and mean cardiac index increased from 2.1 to 2.5 $\text{L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ ($p < 0.05$). Actuarial survival for the 89 patients (exclusive of <30-day or in-hospital mortality, 14%) was 70%, 51%, and 33% at 5, 10, and 15 years. Freedom from reoperation was 93%, 78%, and 68%, and freedom from combined thromboembolism and anticoagulant-related hemorrhage was 82%, 60%, and 50%. These results show that there was no difference in overall survival in patients with dual mechanical valves, dual bioprosthetic valves, or a combina-

tion of both types at 15 years. There was, however, a lower reoperation rate in the group with dual mechanical valves as compared with the group with dual bioprosthetic valves ($p < 0.05$ at 10 years) or with a combination of valves ($p < 0.05$ at 15 years). The higher the number of mechanical valves the higher the combined risk of thromboembolism and anticoagulant-related hemorrhage. Patients who received one or two Starr-Edwards prostheses had significantly higher rates of thromboembolism and anticoagulant-related hemorrhage and a lower survival than those who received other valve combinations. Patients who received two Hancock bioprostheses had significantly higher rates of reoperation and a decreased incidence of combined thromboembolic and anticoagulant-related hemorrhagic events ($p < 0.05$ at 10 years). We conclude that combining a mechanical prosthesis and a bioprosthesis in the same patient is disadvantageous.

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Late results of combined aortic and mitral valve replacement at the same operation using various types of mechanical and bioprostheses have been reported [1-10]. Few reports, however, have compared late results of simultaneous left-sided cardiac valve replacement (as the patient's first cardiac operation) at the same institution using different types of substitute valves [11-26]. The purpose of this study was to determine if the combination of a mechanical aortic and a bioprosthetic mitral valve influences late morbidity and mortality when compared with patients who had dual mechanical or bioprosthetic valves inserted.

Material and Methods

A total of 172 patients underwent simultaneous aortic and mitral valve replacement at the National Heart, Lung and Blood Institute from 1970 to 1989. Eighty-three were excluded from this analysis of late results for the following

reasons: previous cardiac operations, 41; death within 30 days of operation or during initial hospitalization, 24; severe concomitant coronary artery disease, 17; or hypertrophic cardiomyopathy, 1.

The remaining 89 patients form the basis of this report and were separated into five groups based on the types of substitute valves implanted. Thirty-four patients received dual Starr-Edwards ball and cage prostheses (SE-SE, 1970-1984), 14 received a Starr-Edwards aortic prosthesis and a Hancock mitral bioprosthesis (SE-H, 1972-1977), 19 received dual Hancock bioprostheses (H-H, 1975-1984), 12 received a Björk-Shiley tilting-disk aortic prosthesis and a Hancock mitral bioprosthesis (BS-H, 1974-1978), and 10 received dual St. Jude Medical prostheses (SJM-SJM, 1984-1987) (Table 1).

The ages at operation ranged from 15 to 69 years (mean, 50 years); 66% were male. The patients in the SJM-SJM group were younger (41 versus 52 years) than those in the other groups ($p < 0.05$). Six of the 89 patients were less than 30 years of age, and 2 were less than 20 years of age. Sixty-six patients had cardiac catheterization both before (<6 months) and after valve replacement (<9 months).

The 83 patients who were excluded had the following valves implanted (early mortality in parentheses): SJM-SJM, 4 (1); SE-SE, 19 (5); SE-H, 21 (6); BS-H, 12 (5); and

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Table 1. Preoperative Data^a

Group	Substitute Valves (aortic-mitral)	Hospital Survivors	Mean Age (y)	Sex (M/F)	History of:			Mean Duration of Sx (y)	Mean FC (0-4)	Mean PA s/d (mm Hg)	Mean CI (L · min ⁻¹ · m ⁻²)	Type of Valve Lesions					
					History of:							MS + AS	MR + AS	MS + AR	MR + AR		
					ARF	IE	AF										
1	SJM-SJM	10	41 ± 2	7/3	8	2	7	10.2 ± 1.0	3.2 ± 0.0	54/27	2.3 ± 0.1	5	1	1	3		
2	SE-SE	34	52 ± 0	26/8	25	5	24	8.0 ± 0.3	3.0 ± 0.0	56/26	2.1 ± 0.0	17	3	8	6		
3	SE-H	14	53 ± 1	13/1	8	1	8	8.0 ± 0.5	3.1 ± 0.1	51/25	2.0 ± 0.1	4	1	6	3		
4	BS-H	12	52 ± 1	2/10	9	1	7	6.9 ± 0.5	3.1 ± 0.0	61/27	2.2 ± 0.0	6	1	5	0		
5	H-H	19	50 ± 1	11/8	16	1	14	10.4 ± 0.1	3.2 ± 0.0	55/28	2.0 ± 0.0	10	1	5	3		
A (1 + 2)	Mechanical	44	49 ± 2	33/11	33	7	33	8.7 ± 1.4	3.1 ± 0.1	55/26	2.2 ± 0.1	22	4	9	9		
B (3 + 4)	Combined	26	53 ± 2	15/11	17	2	15	7.5 ± 1.3	3.0 ± 0.1	57/25	2.3 ± 0.2	10	2	11	3		
C (5)	Bioprosthetic	19	49 ± 3	11/8	16	1	14	10.4 ± 0.1	3.2 ± 0.1	52/26	1.9 ± 0.1	10	1	5	3		
Total/mean		89	50 ± 0	59/30	66	10	60	8.7 ± 0.1	3.1 ± 0.0	56/26	2.1 ± 0.0	42	7	25	15		
Range/percent			15-69		74%	11%	67%	0.4-44	3.0-4.0	s, 22-100; d, 12-45	1.0-3.8	47%	8%	28%	17%		

^a Data are shown as mean ± standard error of the mean.

AF = atrial fibrillation; AR = aortic regurgitation (pure); ARF = acute rheumatic fever; AS = aortic stenosis; BS = Björk-Shiley (tilting-disc); CI = cardiac index; FC = female; functional class; H = Hancock; M = male; MS = mitral stenosis (with or without regurgitation); IE = infective endocarditis; MR = mitral regurgitation (pure); pressure; s/d = systolic/diastolic; Sx = symptoms of cardiac dysfunction; SE = Starr-Edwards; SJM = St. Jude Medical.

H-H, 27 (7). There were no significant differences between the patients who were excluded because of early death and the remaining 89 patients in terms of the type of valves or combinations of valves that were inserted. Although different valve combinations were placed over different time periods, it is expected that the numerous advances in myocardial protection and surgical technique would have a greater influence on short-term as opposed to long-term survival.

The end of the study was January 1, 1989, and all patients who were still alive were contacted within 2 months of this date. Follow-up was achieved primarily by yearly outpatient clinic visits, the records of which were reviewed. The duration of follow-up per patient ranged from 0.2 to 19 years (mean, 6.6 years), with a total of 583 years for 89 patients (98% complete). Follow-up was incomplete in 3 patients in that it was not known if they were alive or dead at the completion of the study. They were removed from analysis at their last clinic visit and were treated as lost to follow-up, not as having died.

The population of patients of the Surgery Branch of the National Heart, Lung and Blood Institute was unusual in that there was accurate follow-up of all patients in the outpatient clinic every 1 to 2 years for life. All underwent complete preoperative evaluation, and 74% of the 89 patients had a postoperative cardiac catheterization at less than 9 months during a rehospitalization for extensive studies. A physical examination, electrocardiogram, chest radiogram, and echocardiogram were obtained at each clinic visit. Any patient with a change in symptom complex or new echocardiographic findings underwent cardiac catheterization. If a clinic appointment was missed, the patient and the private physician were contacted to find out the status of the patient. Outside cardiac catheterization results were entered into the database as was the cause of death or autopsy results.

Morbidity and mortality results for each group were expressed in both linearized (percent/patient-year) and actuarial terms. Preoperative and postoperative data between groups were compared using unpaired Student's *t* tests, and data within the same group were compared using paired Student's *t* tests. Kaplan-Meier actuarial data were compared by the Mantel-Haenszel test.

Total mortality included all deaths during the follow-up period (Table 2); however, in the actuarial survival analysis, the 3 patients who were lost to follow-up and those who underwent reoperation or who died of trauma or cancer were withdrawn from further analysis on that particular date and were not treated as having died. The actuarial analysis of complications (thromboembolism, anticoagulant-related hemorrhage, and reoperation) included only first events, fatal or nonfatal.

Thromboembolism was defined as any new postoperative neurological or systemic ischemic deficit, whether central or peripheral, temporary or permanent. Patients receiving anticoagulant or antiplatelet agents who had episodes of hemorrhage causing death, stroke, hospitalization, transfusion, or operation were classified as having anticoagulant-related hemorrhage [27]. Those patients taking warfarin but with subtherapeutic prothrombin

Table 2. Postoperative Data^a

Group	Substitute Valves (aortic-mitral)	Hospital Survivors	Total years FU (%)	Mean FC (0-4)	Mean PA		Mean CI (L · min ⁻¹ · m ⁻²)	Warfarin Therapy	Total Mortality (%/y)	Reoperation (%/y)	TE (%/y)		ARH (%/y)	
					s/d (mm Hg)	s/d					Fatal	Total	Fatal	Total
1	SJM-SJM	10	20 (100%)	1.3 ± 0.1	31/14	31/14	2.3 ± 0.1	10 (100%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
2	SE-SE	34	259 (99%)	1.9 ± 0.0	43/18	43/18	2.6 ± 0.0	33 (97%)	26 (10.0%)	2 (0.7%)	5 (1.9%)	10 (3.8%)	1 (0.3%)	4 (1.5%)
3	SE-H	14	69 (90%)	1.9 ± 0.1	35/18	35/18	2.3 ± 0.1	12 (85%)	12 (17.3%)	2 (2.8%)	3 (4.3%)	5 (7.2%)	0 (0.0%)	0 (0.0%)
4	BS-H	12	109 (97%)	1.7 ± 0.1	45/21	45/21	2.3 ± 0.1	4 (21%)	6 (5.5%)	4 (3.6%)	1 (0.9%)	2 (1.8%)	1 (0.9%)	1 (0.9%)
5	H-H	19	125 (100%)	1.4 ± 0.0	36/16	36/16	2.5 ± 0.1	7 (37%)	10 (8.0%)	2 (1.6%)	0 (0.0%)	4 (3.2%)	0 (0.0%)	0 (0.0%)
A (1 + 2)	Mechanical	44	279 (99%)	1.8 ± 0.1	31/14	31/14	2.6 ± 0.1	43 (98%)	26 (9.3%)	2 (0.7%)	5 (1.7%)	10 (3.5%)	1 (0.3%)	4 (1.4%)
B (3 + 4)	Combined	26	178 (95%)	1.9 ± 0.1	43/18	43/18	2.3 ± 0.2	24 (92%)	18 (10.1%)	6 (3.4%)	4 (2.2%)	7 (3.9%)	1 (0.5%)	1 (0.5%)
C (5)	Bioprosthetic	19	125 (100%)	1.3 ± 0.1	36/16	36/16	2.6 ± 0.2	4 (21%)	10 (8.0%)	2 (1.6%)	0 (0.0%)	4 (3.2%)	0 (0.0%)	0 (0.0%)
Total/mean		89	532 (98%)	1.7 ± 0.0	39/17	39/17	2.5 ± 0.0	69 (79%)	54 (9.3%)	10 (1.7%)	9 (1.5%)	21 (3.6%)	2 (0.3%)	5 (0.9%)
Range				1.0 ± 2.5	s, 15-75; d, 10-30		1.8-4.0							

^a Values are shown as mean ± standard error of the mean.

ARH = anticoagulant-related hemorrhage; BS = Björk-Shiley (tilting-disc); SE = Starr-Edwards; SJM = St. Jude Medical; TE = thromboembolism.

FC = functional class; CI = cardiac index; H = Hancock; PA = pulmonary artery pressure; s/d = systolic/diastolic.

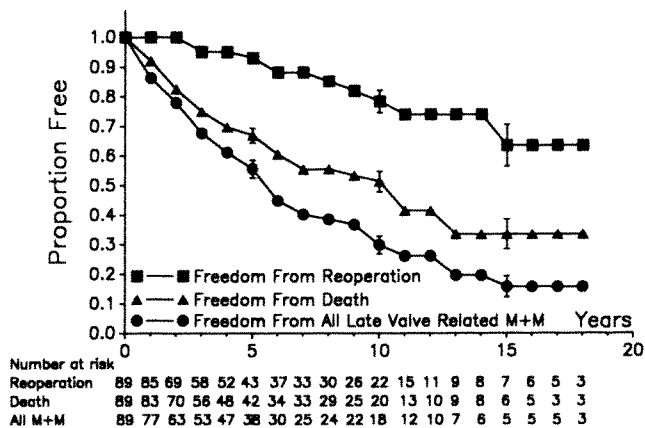


Fig 1. Actuarial curves of freedom from reoperation, death, and all valve-related late morbidity and mortality (M+M) in 89 hospital survivors of combined aortic and mitral valve replacement.

times at the time of a morbid event were classified as having a thromboembolic event rather than an anticoagulant-related hemorrhage. In the patients receiving warfarin, a prothrombin time of 1.5 to 2 times normal was recommended.

Valve-related morbidity and mortality includes all late deaths, reoperations, thromboembolism, and anticoagulant-related hemorrhage. The 6 patients who died in congestive heart failure with normal valves and those who died of cancer or trauma were specifically excluded at the time of their deaths. Note that this is a measure of valve-related late morbidity and mortality and specifically excludes less than 30-day and in-hospital mortality, which was 13% (8% for reoperations and 5% for the initial operation). In the group of patients who were excluded because of early mortality, only 1 of 24 patients (with an H-H valve combination) had a thromboembolic event at less than 30 days and eventually died of pneumonia.

Results

No differences in frequency of rheumatic fever, infective endocarditis, or atrial fibrillation, duration of symptoms of cardiac dysfunction, functional class, mean preoperative pulmonary arterial pressure, cardiac index, or distribution of types of hemodynamic valvular lesions were noted among the five groups of patients (see Table 1). When the data were combined into three groups consisting of patients with dual mechanical valves, a mechanical aortic valve plus a bioprosthetic mitral valve, and dual bioprosthetic valves, there were no differences in the above parameters (see Table 1).

Survival

The actuarial survival for the 89 patients (exclusive of in-hospital or <30-day morbidity) was 92%, 70%, 51%, and 33% at 1, 5, 10, and 15 years (Fig 1). The mean postoperative functional class of all five groups decreased from 3.3 to 1.7 ($p < 0.05$), pulmonary arterial pressure decreased from 56/26 to 39/19 mm Hg ($p < 0.05$), and

cardiac index increased from 1.7 to $2.1 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ ($p < 0.05$). When the data were grouped according to patients with dual mechanical valves versus dual bioprosthetic valves or a combination of a mechanical and a bioprosthetic valve, there were significant decreases in pulmonary pressures and improvements in functional class in all groups, without differences between the groups ($p < 0.05$). The cardiac index significantly increased in the groups with either dual mechanical or dual bioprosthetic valves ($p < 0.05$) but did not significantly increase postoperatively in the group with combined mechanical and bioprosthetic valves (see Table 2).

The actuarial survival of the SE-H group at 5 and 10 years was 56% and 14% and was lower than that of the other groups ($p < 0.05$). At 10 years, the survival of the patients with one or two Starr-Edwards prostheses was lower than that of the other three groups followed up for at least 10 years ($p < 0.05$). At 3 years, the actuarial survival in the SJM-SJM group was 100%, which was higher than that of the other four groups ($p < 0.05$) (Fig 2). When the patients were reorganized into groups with dual mechanical valves, dual bioprosthetic valves, or one of each, there were no differences in actuarial survival between any of the groups at 10 years (51%) (Fig 3) or in percent deaths per 100 patient-years (8% to 10%) (see Table 2).

Fifty-four patients had died by the end of the follow-up period, 29 of whom underwent autopsy. Eleven of these patients died of consequences of strokes, believed to result from emboli in 9 and from intracerebral hemorrhage in 2 (while taking warfarin). The others died of chronic congestive heart failure without evidence of valvular dysfunction (1), acute myocardial infarction (4), lung cancer (5), trauma (2), and after reoperation to replace or repair one or both left-sided prosthetic valves (6). Three of the later patients died in the hospital and the other 3 died at some later date. The other 25 patients who were without autopsies were not specifically thought to have

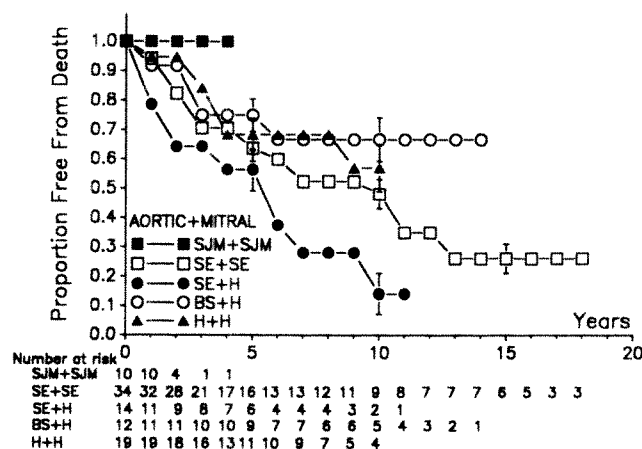


Fig 2. Comparison of actuarial curves of freedom from death in 89 hospital survivors of combined aortic and mitral valve replacement with five different combinations of substitute valves. (BS = Björk-Shiley [tilting-disc]; H = Hancock; SE = Starr-Edwards; SJM = St. Jude Medical.)

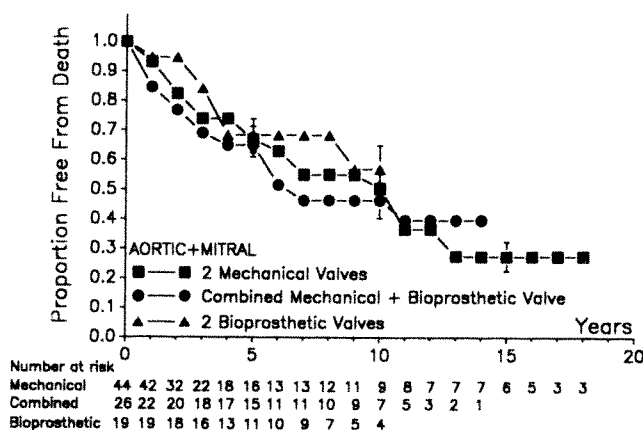


Fig 3. Comparison of actuarial curves of freedom from death in 89 hospital survivors of combined aortic and mitral valve replacement with three different combinations of substitute valves: mechanical, bioprosthetic, and a combination of the two.

died of any of the above problems and were treated as valve-related mortality.

Reoperation

Actuarial freedom from reoperation for all 89 patients was 100%, 93%, 78%, and 68% at 1, 5, 10, and 15 years (see Fig 1). Forty-five bioprostheses were inserted, of which 5 (11%) were removed for structural deterioration. There were no differences in reoperation at 5 years among groups (Fig 4); however, at greater than 10 years, the SE-SE group had a higher freedom from reoperation than those groups with one or two bioprosthetic valves ($p < 0.05$) (see Fig 4). There was a higher freedom from reoperation at greater than 10 years in the group with two mechanical valves compared with the groups with the combination of a mechanical and a bioprosthetic valve or dual bioprosthetic valves ($p < 0.05$) (Fig 5). The patients with SJM-SJM prostheses were free from reoperation at 3 years.

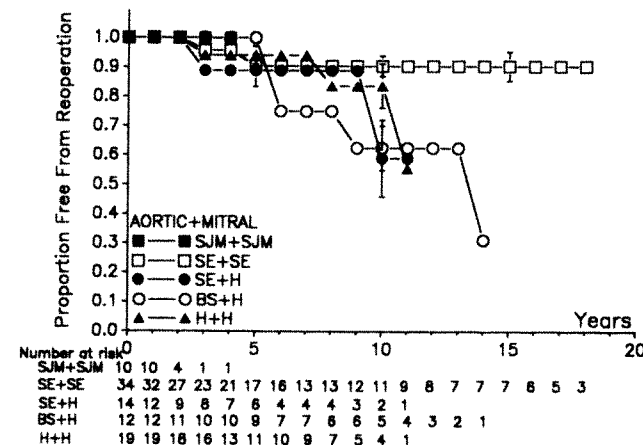


Fig 4. Comparison of actuarial curves of freedom from reoperation in 89 hospital survivors of combined aortic and mitral valve replacement with five different combinations of substitute valves. (BS = Björk-Shiley [tilting-disc]; H = Hancock; SE = Starr-Edwards; SJM = St. Jude Medical.)

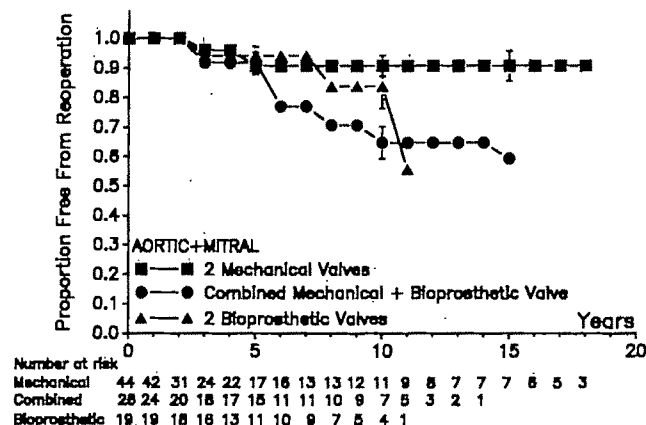


Fig 5. Comparison of actuarial curves of freedom from reoperation in 89 hospital survivors of combined aortic and mitral valve replacement with three different combinations of substitute valves: mechanical, bioprosthetic, and a combination of the two.

Reoperation was performed in 10 (11%) of the 89 patients, a frequency of 1.7 per 100 patient-years (Table 3). In the SE-SE group, 2 of 34 patients underwent reoperation: 1 had severe hemolytic anemia due to prosthetic cloth wear and 1 had a perivalvular leak. In the SE-H group, 2 of 14 patients underwent reoperation: 1 had structural deterioration of the Hancock mitral bioprosthesis and 1 had aortic and mitral perivalvular leaks. In the BS-H group, 4 of 12 patients had reoperation: 3 patients had structural deterioration of the Hancock bioprostheses in the mitral position and 1 patient had a mitral perivalvular leak and aortic prosthetic valve thrombus. In the H-H group, 2 of 19 patients underwent reoperation, 1 patient for structural deterioration of the Hancock mitral bioprosthesis and 1 patient for infective endocarditis involving both bioprostheses.

Thromboembolism

Actuarial freedom from combined thromboembolism and anticoagulant-related hemorrhage for the 89 patients was 87%, 82%, 60%, and 50% at 1, 5, 10, and 15 years (Fig 6). At 5 and 10 years, freedom from these events was 92% and 71% in the BS-H group, 89% and 75% in the H-H group, 67% and 45% in the SE-H group, and 72% and 55% in the SE-SE group. Freedom from these events at 15 years was 40% in the SE-SE group and 71% in the BS-H group. The differences among the groups did not achieve statistical significance at 5 years (Fig 7). The patients with one or two Starr-Edwards prostheses, however, had a significantly higher frequency of combined thromboembolism and anticoagulant-related hemorrhage when compared with the other groups at 10 years ($p < 0.05$) (see Fig 7). When the groups were compared according to mechanical valves, bioprosthetic valves, or a combination of the two types, there were no differences at 5 years; however, the three groups were significantly different from each other at 10 years. The group with dual mechanical valves had a higher incidence of thromboembolic and anticoagulant-related events than did the group with one mechanical

Table 3. Cardiac Morphologic Findings in Ten Patients Who Underwent Reoperation After Initial Combined Mitral and Aortic Valve Replacement

Patient No.	Age (y)	Sex	Initial Substitute Valves		Interval From First to Second Operation (y)	Abnormal Cardiac Morphologic Findings		Type of Reoperation			Death Early (<30 d) ^a
			Aortic	Mitral		Aortic	Mitral	AVR	MVR	TVR	
1	54	M	SE	SE	2.8	...	Peribasilar leak	0 ^b	0	+	+
2	58	M	SE	SE	4.8	Peribasilar leak	Cloth wear	+	+	0 ^b	0
3	53	M	SE	H	2.5	Peribasilar leak	Peribasilar leak	+	+	0 ^b	0
4	36	M	SE	H	10.0	...	Cuspal tear, CD	0	+	+	0
5	49	F	BS	H	5.4	...	Cuspal deterioration	0	+	0 ^b	0
6	49	F	BS	H	5.4	Disc thrombus	Peribasilar leak	+	+	0	0
7	61	F	BS	H	7.6	...	Cuspal tear, CD	0	+	0	0
8	46	M	BS	H	14.2	...	Cuspal tear, CD	0	+	0	+
9	39	F	H	H	5.8	...	Cuspal tear	+	+	0	0
10	39	F	H	H	10.4	IE	IE	+	+	+	+
Total								5	9	3	3
Percent								(50%)	(90%)	(30%)	(30%)

^a Or before hospital discharge. ^b Valvular repair. ^c Prophylactic aortic valve replacement.

AVR = aortic valve replacement; BS = Björk-Shiley (tilting-disc); CD = calcific deposits; IE = infective endocarditis; M = male; MVR = mitral valve replacement; SE = Starr-Edwards; TVR = tricuspid valve replacement.

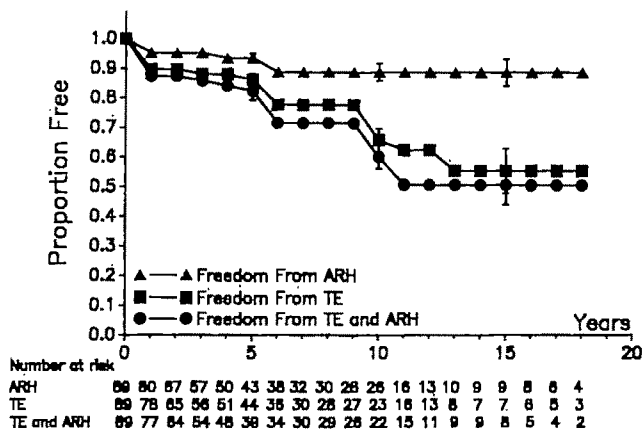


Fig 6. Actuarial curves of freedom from thromboembolism (TE), anti-coagulant-related hemorrhage (ARH), and combined TE and ARH in 89 hospital survivors of combined aortic and mitral valve replacement.

valve, which had a higher incidence of thromboembolic events than the group with dual bioprostheses ($p < 0.05$) (Fig 8).

Thromboembolism occurred in 21 patients (3.6 per 100 patient-years). Nine events were fatal (1.5 per 100 patient-years). The frequency of thromboembolism per 100 patient-years was 7.2 in the SE-H group, 3.8 in the SE-SE group, 3.2 in the H-H group, and 1.8 in the BS-H group. No thromboembolic events occurred in the SJM-SJM group during 20 patient-years of observation. The actuarial curve of thromboembolism was significantly lower than that of anticoagulant-related hemorrhage at 10 years (60% versus 90%; $p < 0.05$) (see Fig 6). The actuarial curves of first thromboembolism alone paralleled the incidence of combined thromboembolism and anticoagulant-related hemorrhage (Fig 9; see Fig 7). Patients with one or two Starr-Edwards valves had a lower freedom

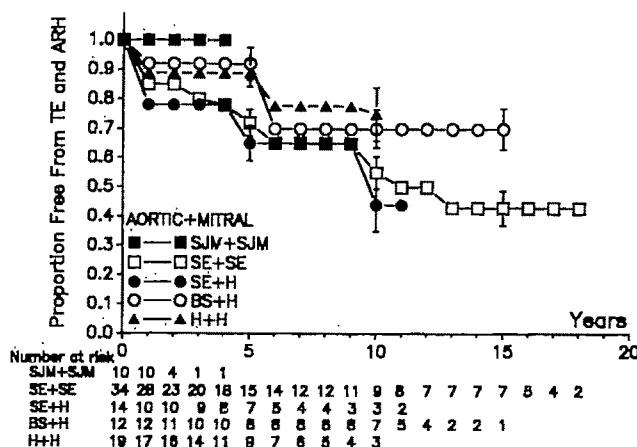


Fig 7. Comparison of actuarial curves of freedom from combined thromboembolism (TE) and anticoagulant-related hemorrhage (ARH) in 89 hospital survivors of combined aortic and mitral valve replacement with five different combinations of substitute valves. (BS = Björk-Shiley [tilting-disc]; H = Hancock; SE = Starr-Edwards; SJM = St. Jude Medical.)

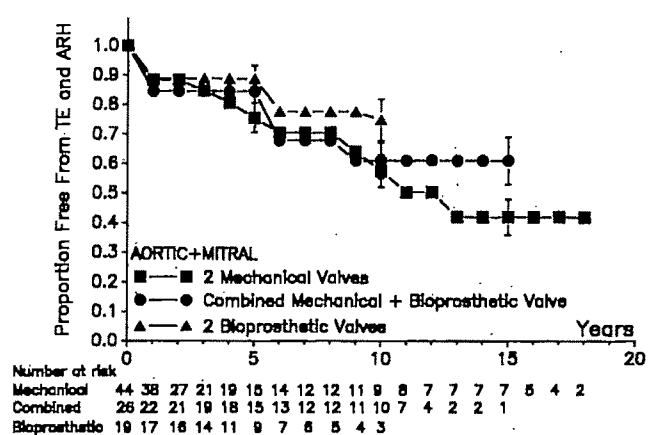


Fig 8. Comparison of actuarial curves of freedom from combined thromboembolism (TE) and anticoagulant-related hemorrhage (ARH) in 89 hospital survivors of combined aortic and mitral valve replacement with three different combinations of substitute valves: mechanical, bioprosthetic, and a combination of the two.

from thromboembolism than the other groups at 10 years ($p < 0.05$). When the groups were compared according to mechanical valves, bioprosthetic valves, or a combination of the two types, there were no differences in thromboembolism at 10 years (Fig 10).

Anticoagulant-Related Hemorrhage

Anticoagulant-related hemorrhage occurred in 5 patients (0.9 per 100 patient-years) with two fatalities. Four of the five hemorrhagic events occurred in patients with SE-SE prostheses, with one event in a patient with BS-H valves. The SJM-SJM and H-H groups had significantly fewer thromboembolic and anticoagulant-related events than the other valve groups (Figs 11, 12; see Fig 6). The decreased incidence of anticoagulant-related hemorrhage in the H-H group by definition is going to be low because very few patients in that group were receiving warfarin.

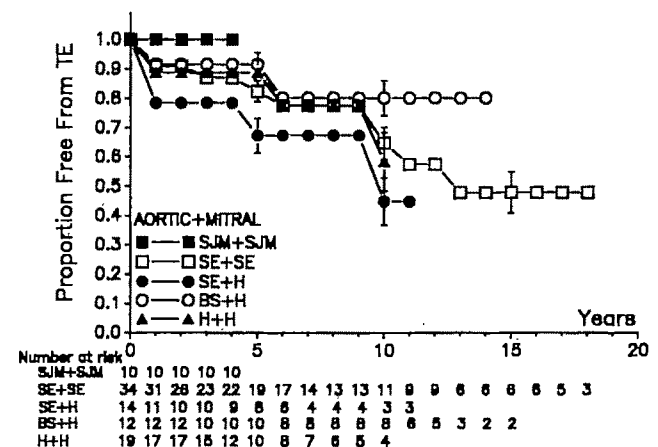


Fig 9. Comparison of actuarial curves of freedom from thromboembolism (TE) in 89 hospital survivors of combined aortic and mitral valve replacement with five different combinations of substitute valves. (BS = Björk-Shiley [tilting-disc]; H = Hancock; SE = Starr-Edwards; SJM = St. Jude Medical.)

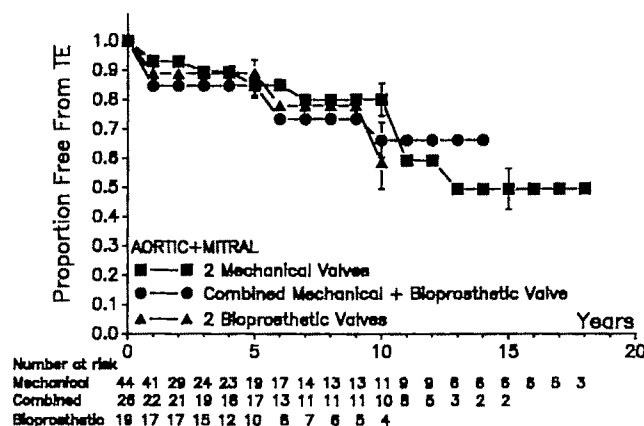


Fig 10. Comparison of actuarial curves of freedom from thromboembolism (TE) in 89 hospital survivors of combined aortic and mitral valve replacement with three different combinations of substitute valves: mechanical, bioprosthetic, and a combination of the two.

Valve-related late morbidity and mortality paralleled the incidence of total survival (Fig 13; see Fig 1). There was no difference in overall valve-related late morbidity and mortality between the dual bioprosthetic, dual mechanical, and combined valve replacement groups (Fig 14).

Sixty-nine patients took warfarin after operation: all patients in the SJM-SJM and BS-H groups, 33 of 34 in the SE-SE group, 12 of 14 patients in the SE-H group, and 4 of 19 patients in the H-H group. The patients with Starr-Edwards valves in place who did not take warfarin did so secondary to severe bleeding problems or noncompliance. The patients in the H-H group took warfarin because of atrial fibrillation or a history of strokes.

Comment

Simultaneous aortic and mitral valve replacement has been performed for many years, but, in almost all large

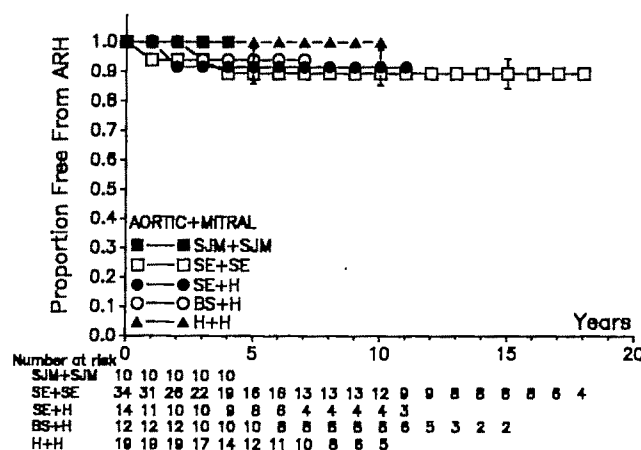


Fig 11. Comparison of actuarial curves of freedom from anticoagulant-related hemorrhage (ARH) in 89 hospital survivors of combined aortic and mitral valve replacement with five different combinations of substitute valves. (BS = Björk-Shiley [tilting-disc]; H = Hancock; SE = Starr-Edwards; SJM = St. Jude Medical.)

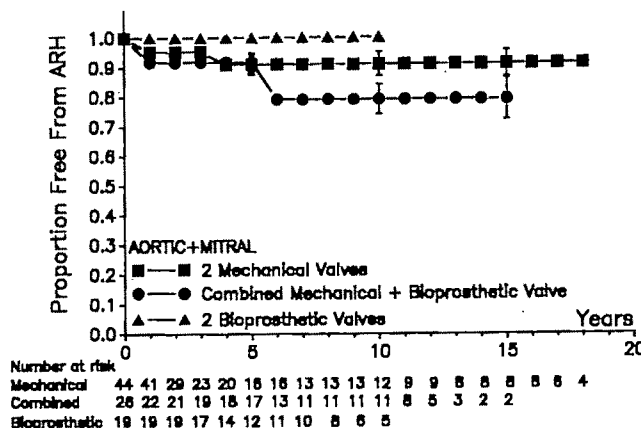


Fig 12. Comparison of actuarial curves of freedom from anticoagulant-related hemorrhage (ARH) in 89 hospital survivors of combined aortic and mitral valve replacement with three different combinations of substitute valves: mechanical, bioprosthetic, and a combination of the two.

series of patients, the combination of a mechanical and a bioprosthetic valve is still reported (10% to 15%). The reasons for the combination are unclear. At the National Institutes of Health, it was thought that a bioprosthetic valve in the aortic position would not last as long as in the mitral position. Although the converse has turned out to be the case, that reasoning has certainly played a role in not inserting bioprosthetic valves in the aortic position but does not explain why a mechanical valve was not placed in the mitral position. There is no scientific basis for mixing prosthetic types unless some anatomical constraint noted at the time of operation necessitated a particular valve type, which should be a rare occurrence. Combining a mechanical and a bioprosthetic valve requires the patient to undergo long-term anticoagulation as

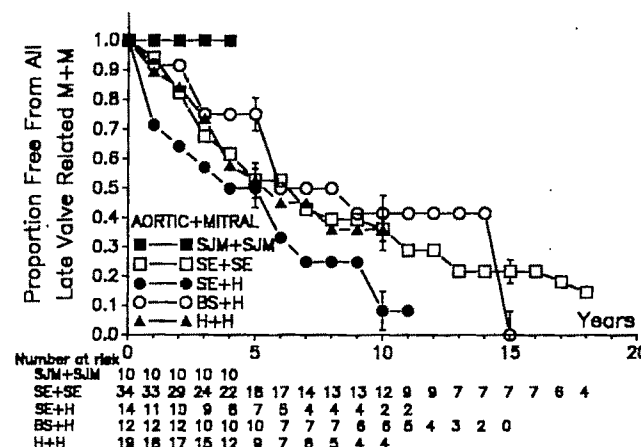


Fig 13. Comparison of actuarial curves of all valve-related mortality and morbidity (M+M) (freedom from death, reoperation, thromboembolism, and anticoagulant-related hemorrhage) in 89 hospital survivors of combined aortic and mitral valve replacement with five different combinations of substitute valves. (BS = Björk-Shiley [tilting-disc]; H = Hancock; SE = Starr-Edwards; SJM = St. Jude Medical.)

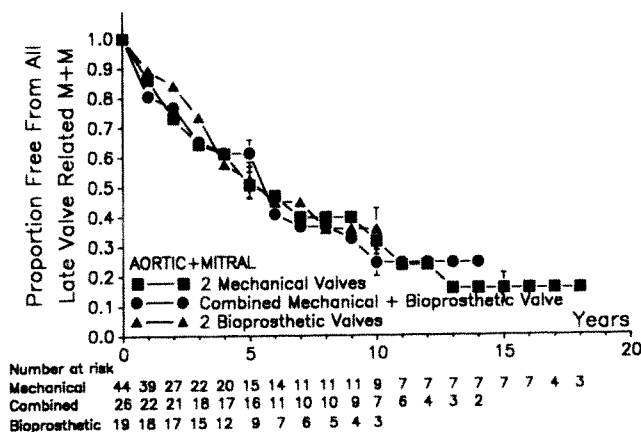


Fig 14. Comparison of actuarial curves of all valve-related mortality and morbidity (M+M) (freedom from death, reoperation, thromboembolism, and anticoagulant-related hemorrhage) in 89 hospital survivors of combined aortic and mitral valve replacement with three different combinations of substitute valves: mechanical, bioprosthetic, and a combination of the two.

well as a possible second operation for structural deterioration.

This study indicates that, during the first year after combined aortic and mitral valve replacement with any of the five substitute valves, decreased pulmonary arterial pressure, increased cardiac index, and improved functional class are achieved. These results show that there was no difference in overall survival or valve-related late morbidity or mortality between mechanical, bioprosthetic, and combined double-valve replacement at 15 years. There was, however, a lower reoperation rate in the groups with two mechanical valves than in the other two groups, and the higher the number of mechanical valves (excluding SJM-SJM), the higher the risk of combined thromboembolism and anticoagulant-related hemorrhage at 10 years. The groups with dual porcine valves had a higher rate of reoperation and a decreased combined incidence of thromboembolism and anticoagulant-related hemorrhage. The incidence of thromboembolism was the same in the three groups. Patients who received one or two Starr-Edwards prostheses had significantly higher rates of reoperation and combined thromboembolism and anticoagulant-related hemorrhage with a lower survival than those with other valve combinations.

Two previous reports from this institution have compared preoperative and postoperative hemodynamic data after combined aortic and mitral valve replacement. In the first report in 1967, Mason and associates [15] described a marked postoperative decrease in pulmonary arterial pressure and increase in cardiac output in the 12 patients studied. Melvin and associates [16] in 1973 analyzed preoperative and postoperative prognostic factors in 100 patients with combined aortic and mitral valve replacement, finding lower long-term survival in older patients and in those with elevated pulmonary arterial pressures, but no difference in terms of the types of valves that were placed. The operations in that study were performed

between 1963 and 1970, whereas the interval of study in the present group of patients was 1970 to 1989.

Several reports of late results of combined aortic and mitral valve replacement are available (Table 4), but most are not comparable with this study because of variance of inclusion criteria, duration and completeness of follow-up, and presentation of morbidity and mortality data. Armenti and associates [17] in 1987 reported results of combined aortic and mitral valve replacement with the SJM-SJM combination in 92 patients with a mean follow-up period of 2.8 years. Actuarial survival at 3 and 5 years was 76% and 62%, respectively. Linearized rates of thromboembolism and anticoagulant-related hemorrhage were 4.6%/year and 1.2%/year, and reoperation was performed at a rate of 2.1%/year. Thromboembolism was the most common complication after insertion of the SJM-SJM combination in that study. The absence of morbidity and mortality in our 10 patients with the SJM-SJM combination may be due in part to the small number of patients, the younger mean age at operation, the recent dates of operation and short follow-up period (mean, 2 years), and meticulous attention to anticoagulation regulation.

Bortolotti and associates [18] in 1987 reported late results after combined aortic and mitral valve replacement with dual Hancock bioprostheses in 55 patients with a mean follow-up of 5.7 years. Ten-year survival of hospital survivors was 54%, compared with 68% in our smaller group (14 patients) with dual Hancock bioprostheses. Thromboembolism occurred in 1.3%/year, compared with 3.2%/year in our group, and reoperation was performed in 3.5%/year, compared with 1.6%/year in our group. Bortolotti and associates [19] in 1988 published late results of simultaneous insertion of a mechanical aortic prosthesis and a porcine mitral bioprosthesis in 76 patients. Rates of thromboembolism, anticoagulant-related hemorrhage, and reoperation were higher than when dual bioprostheses were used.

Bortolotti and associates [20] in this journal in 1991 reported on the influence of type of prosthesis on late results after combined mitral and aortic valve replacement. Using 14 different valve combinations over 14 years, they concluded that there was no difference in survival, thromboembolism, or anticoagulant-related hemorrhage between mechanical, biological, or mixed replacements strategies. They also showed that the reoperation rate was lowest in the groups with dual mechanical valves as compared with the group with dual bioprosthetic valves or a combination of a mechanical and a bioprosthetic valve. Our data agree with these findings in that there was no difference in survival between groups, and the higher the number of bioprosthetic valves, the higher the reoperation rate. However, our data did show that the more mechanical valves that were used, the higher the incidence of anticoagulant-related hemorrhage, but this was largely influenced by the SE-SE group and the fact that patients with dual bioprosthetic valves are less likely to be anticoagulated.

Our data also support the continued practice of using a St. Jude Medical prosthesis in both positions when anticoagulation is not contraindicated. The patients with a

Table 4. Previously Reported Late Results of Combined Aortic and Mitral Valve Replacement After 1980

First Author	Reference	Year Published	Substitute Valve Combination (aortic-mitral)	No. of Patients	Mean FU (y)	10-Year Survival (%)		Reoperation (%/y)	TE (%/y)	ARH (%/y)
						All	Hospital Survivors ^a			
Dual mechanical valves										
Stephenson	11	1984	SJM-SJM	52	1.5	...	...	...	3.9	1.3
Czer	13	1987	SJM-SJM	52	...	...	...	...	3.4	3.4
Armenti	17	1987	SJM-SJM	92	2.8	...	...	0.8	4.6	1.2
Brown	... ^b	1993	SJM-SJM	10	2.1	...	...	0.0	0.0	0.0
Teply	23	1981	SE-SE	253	...	45	...	...	...	...
Stephenson	11	1984	SE-SE	19	5.2	...	...	...	4.0	2.0
Fessatidis	24	1987	SE-SE	46	...	...	81	1.7	5.2	0.4
Brown	... ^b	1993	SE-SE	34	7.6	...	48	0.7	3.8	1.5
Stephenson	11	1984	BS-BS	35	4.6	...	...	...	2.5	1.2
Flemma	25	1988	BS-BS	55	9.1	...	65	...	1.2	...
Nitter-Hauge	26	1989	MH-MH	101	4.5	60	...	0.2	2.0	0.7
Mikaeloff	14	1988	BS-mv	322	7.0	70	...	0.7	3.4	2.2
Bortolotti	20	1991	mv-mv	221	6.4	40	60	1.0	1.9	1.3
Brown	... ^b	1993	mv-mv	44	6.3	...	50	0.7	3.5	1.4
Combined mechanical and bioprosthetic valves										
Brown	... ^b	1993	SE-H	14	4.9	...	14	2.8	7.2	0.0
Brown	... ^b	1993	BS-H	12	9.1	...	66	3.6	1.8	0.9
Bortolotti	19	1988	mv-H	76	7.0	...	58	4.4	1.6	2.3
Brown	... ^b	1993	mv-H	26	6.6	...	46	3.4	3.9	0.5
Bortolotti	20	1991	mv-bpv	97	9.1	35	52	4.4	1.7	0.8
Dual bioprosthetic valves										
Stephenson	11	1984	H-H	32	3.8	...	...	...	2.5	0.0
Bortolotti	18	1987	H-H	55	5.7	...	54	3.5	1.3	1.3
Cohn	28	1989	H-H	146	6.0	58	...	...	...	...
Brown	... ^b	1993	H-H	19	6.6	...	57	1.6	3.2	0.0
Czer	13	1987	bpv-bpv	23	...	...	...	...	1.0	2.0
Bortolotti	20	1991	bpv-bpv	135	6.0	29	46	6.1	1.6	1.6

^a Hospital survivors or survival >30 days. ^b Present study.

ARH = anticoagulant-related hemorrhage; bpv = bioprosthetic valve; BS = Björk-Shiley (tilting-disc); FU = follow-up; H = Hancock; MH = Medtronic-Hall; mv = mechanical valve; SJM = St. Jude Medical; TE = thromboembolism.

bioprosthetic mitral valve and a mechanical aortic valve have the same long-term survival as those with dual mechanical or bioprosthetic valves but have a reoperation rate that is worse than the dual mechanical valve group and equal to the dual bioprosthetic valve group. The incidence of the combined thromboembolism and anticoagulant-related hemorrhage is higher than that of the dual bioprosthetic valve group but less than that of the dual mechanical valve group. The practice of combining a bioprosthesis and a mechanical prosthesis should be discouraged, as this combination imparts the disadvantages of both valve types and the advantages of neither, especially if the patient requires anticoagulation for reasons other than for a mechanical valve [21, 22]. Meticulous attention should be paid to regulation of anticoagulation as 60% of the thromboembolic and 80% of the anticoagulant-related hemorrhagic events occurred when the prothrombin time was subtherapeutic or supratherapeutic, respectively.

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Open Mitral Commissurotomy: Fourteen- to Eighteen-Year Follow-up Clinical Study

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From May 1974 to December 1978, 159 patients with mitral stenosis underwent open mitral commissurotomy at our institution. Follow-up data were complete in 96.8%, with a mean follow-up of 13.7 years (range, 14 to 18 years). Preoperatively, most patients ($n = 94$) were in functional class III or IV. Valve calcification was found in 18 patients (11.3%), left atrial thrombosis was found in 21 (13.2%), and the subvalvular apparatus was affected in 105 (66%). When a residual insufficiency was detected during the operation, a mitral annuloplasty was performed ($n = 43$). There was one hospital death (0.6%) and 15 late deaths (9.5%). Actuarial survival at 15-year and 18-year follow-up is $89.4\% \pm 3\%$ and $75.2\% \pm 10.8\%$. Fifteen patients (9.7%) had a thromboembolic episode 1

to 189 months after operation (mean, 104.3 months). Eleven patients (7%) required reoperation 3 to 183 months after operation (mean, 110.1 months). Freedom from reoperation at 18-year follow-up was $91.9\% \pm 2.7\%$. Event-free actuarial survival at 15-year and 18-year follow-up was $73.4\% \pm 4.2\%$ and $54.3\% \pm 10.5\%$. Most patients ($n = 131$) are in class I or II. Open mitral commissurotomy represents a safe surgical alternative for treating mitral stenosis, allowing a complete removal of atrial thrombosis if present. This long-term follow-up clinical study encourages us to persist in this successful surgical repair of mitral stenosis.

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Numerous reports have been published demonstrating the efficiency of closed mitral commissurotomy for the surgical treatment of pure mitral stenosis [1-5]. Different authors [6-8] have advocated routine use of the open technique as the method of choice. In 1980, controversy still remained about the best approach to mitral commissurotomy, so we published our early results in 163 consecutive patients with pure mitral stenosis who underwent open mitral commissurotomy (OMC) [9]. Currently, a new controversy has emerged regarding OMC versus percutaneous valvuloplasty. We here retrospectively analyzed the long-term follow-up in OMC with the same series of patients previously reported [9].

Material and Methods

From May 1974 to December 1978, 159 patients with pure mitral stenosis underwent OMC at our institution. Mean age was 41.5 years (range, 13 to 65 years), and 78% of the patients were female. Preoperatively 59% were in New York Heart Association functional class III or IV. Preoperative thromboembolic phenomena were recorded in 44 patients (27.8%). Nine had a previous closed mitral commissurotomy.

All patients had a preoperative hemodynamic study except 2 who required an emergency operation. Systolic pulmonary artery pressure ranged from 25 to 150 mm Hg

(mean, 45.7 mm Hg), the mitral gradient ranged from 8 to 32 mm Hg (mean, 17.2 mm Hg), the cardiac index ranged from 1.5 to $6.7 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ (mean, $2.8 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$), and the total pulmonary resistance ranged from 168 to 2,853 dynes $\cdot \text{s} \cdot \text{cm}^{-5}$ (mean, 563 dynes $\cdot \text{s} \cdot \text{cm}^{-5}$).

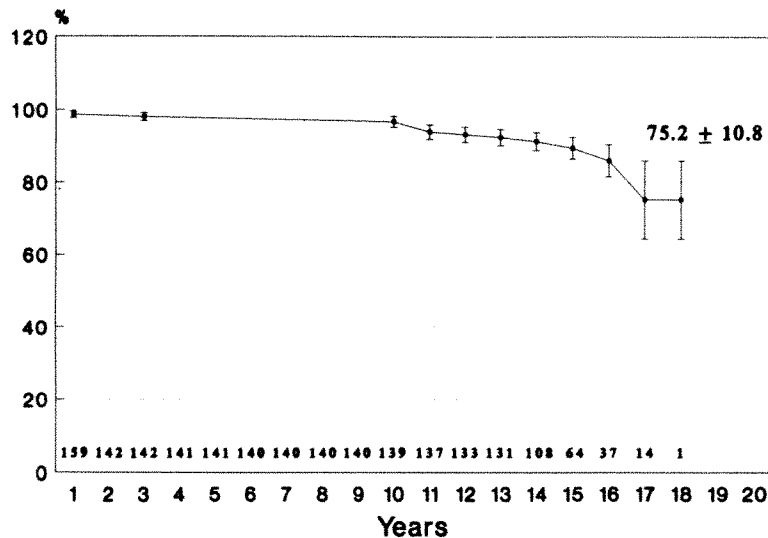
All the patients were operated on with conventional extracorporeal circulation using a bubble oxygenator, hypothermia, and, since 1977, coronary perfusion with a cold crystalloid cardioplegic solution. In every patient, after commissurotomy the valvular competence was tested by injecting blood from the extracorporeal pump through a left-vent cannula [10]. Calcification in the valve was found in 18 patients (11.3%) and left atrial thrombus in 21 patients (13.2%). The subvalvular apparatus was affected in 66% of the patients. The operative procedures were isolated commissurotomy in 51 patients; mitral commissurotomy and splitting of papillary muscles in 65; mitral commissurotomy and annuloplasty in 10; and mitral commissurotomy, splitting of papillary muscles, and annuloplasty in 33 patients. Open mitral commissurotomy was successfully performed in 116 patients (71.1%) with pure mitral stenosis. Mitral annuloplasty was performed using a Duran flexible ring in 36 patients, a Carpentier ring in 5 patients, and the Wooler technique in 2 patients. All patients with atrial fibrillation with preoperative thromboembolism or presence of atrial thrombus received long-term oral anticoagulant therapy. This was permanent in patients with giant left atrium or atrial thrombosis.

The follow-up was complete in 96.8% from January through July 1991 with an average of 13.7 years (range, 14

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Fig 1. Actuarial survival curve of 159 patients undergoing open mitral commissurotomy. Numbers below curve indicate population at risk during follow-up.



to 18 years). All elements of data collection were subjected to computer analysis. Chi-square test and Student's *t* test were used for analysis of significance. Survival and cumulative incidence curves were obtained by the actuarial method. Several preoperative factors were examined for their predictive value of the need for reoperation, late death, and postoperative functional class. These factors were age, preoperative functional class and pulmonary resistance, presence of atrial fibrillation, preoperative thromboembolism, presence of left atrial thrombus, mitral valve calcification, papillotomy, and annuloplasty.

Results

Hospital Mortality

A 60-year-old patient with severe pulmonary hypertension died 20 days postoperatively as a consequence of respiratory failure, being the only patient lost early after operation (0.6%).

Late Mortality

Late death occurred in 15 patients (9.5%) due to thromboembolism (*n* = 1), noncardiac causes (*n* = 2), sudden death (*n* = 1), and at home of unknown origin (*n* = 11).

Actuarial survival at 15-year and 18-year follow-up is $89.4\% \pm 3\%$ and $75.2\% \pm 10.8\%$, respectively (Fig 1).

Thromboembolism and Anticoagulant-Related Hemorrhage

Fifteen patients (9.7%) had thromboembolic episodes: 6 central with total recovery and 9 peripheral. Thromboembolic events occurred 1 to 189 months after operation (mean, 104.3 months). Four patients were in atrial fibrillation and none were anticoagulated when the event occurred. The actuarial freedom from thromboembolic events is $88.2\% \pm 3.2\%$ and $84.3\% \pm 4.9\%$ at 15-year and 18-year follow-up, respectively (Fig 2). Four of 24 patients (16.7%) receiving permanent anticoagulation had hemor-

Fig 2. Actuarial curve of freedom from thromboembolism.

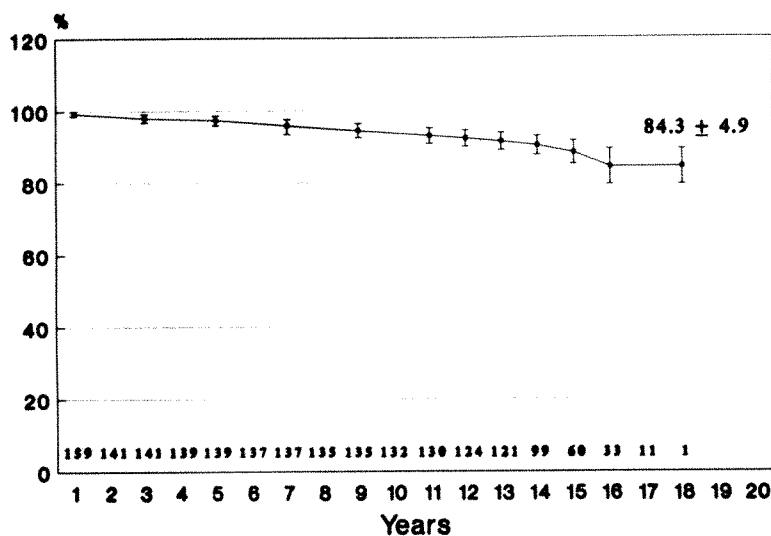


Table 1. Causes of Reoperation and Procedures Performed in the 11 Patients Having Reoperation

Pathology	No. of Patients	Procedure	No. of Patients
MS	4	MVR	2
		Redo OMC	2
MI	1	MVR	1
Mixed ML + CAD	1	MVR + CABG	1
MS + AS	1	MAVR	1
Mixed ML + AS	1	MAVR	1
MS + TI	1	MVR + TA	1
MI + TI	1	MVR + TA	1
TI	1	TA	1

AS = aortic stenosis; CABG = coronary artery bypass grafting; CAD = coronary artery disease; MAVR = mitral and aortic valve replacement; MI = mitral insufficiency; MS = mitral stenosis; MVR = mitral valve replacement; Mixed ML = mixed mitral lesion; OMC = open mitral commissurotomy; TA = tricuspid annuloplasty; TI = tricuspid insufficiency.

rhagic complications: 3 minor external and 1 internal bleeding controlled by medical treatment.

Reoperations

Eleven patients (7%) required reoperation 3 to 183 months after operation (mean, 110.1 months). Causes of reoperation were structural deterioration in 9 patients (restenosis in 5, insufficiency in 2, and mixed mitral lesion in 2 patients), valve endocarditis in 1 patient, and severe tricuspid incompetence in 1 patient (Table 1).

Mitral commissurotomy was successfully performed at reoperation in 2 patients, and valve replacement was necessary in 8 patients (bioprosthesis in 3 and mechanical valve in 5). The remaining patient required Duran flexible ring annuloplasty. Concomitant aortic valve replacement was performed in 2 patients, tricuspid annuloplasty in 2, and coronary artery bypass grafting in 1 patient. Freedom from reoperation in this series is $91.9\% \pm 2.7\%$ and 88.4%

$\pm 4.3\%$ at 15-year and 18-year follow-up, respectively (Fig 3).

Event-free actuarial survival at 15-year and 18-year follow-up was $73.4\% \pm 4.2\%$ and $54.3\% \pm 10.5\%$, respectively (Fig 4). This incidence does not include nonrelated mitral valve reoperation ($n = 1$) and noncardiac deaths ($n = 2$).

Functional Class

Postoperatively, 60 of the surviving patients (41.6%) were asymptomatic, 71 patients (50%) in class II, 8 patients (5.6%) in class III, and 4 patients (2.8%) in class IV. Most patients in class III or IV ($n = 11$) underwent reoperation. Actually, only 1 patient remains in class III due to severe coronary artery disease.

Preoperative Risk Factors

As shown in Table 2, the age at the time of operation and the presence of atrial thrombosis were risk factors achieving significance ($p < 0.01$) for late mortality. Associated mitral annuloplasty represented a risk factor for postoperative thromboembolism ($p < 0.001$). Patients who died were older than the surviving patients (mean age, 50.4 years versus 38 years) and had a greater incidence of left atrial thrombosis (38.5% versus 10.3%).

Comment

As we previously reported with the same group of patients [9], OMC can be carried out with a low hospital mortality, similar to or lower than that of the closed mitral approach [1, 2, 11-14] and that of percutaneous mitral valvuloplasty [15]. The open technique allows the surgeon to work under direct vision, repair fused chordae tendineae and papillary muscles, debride the localized calcium nodules, and perform annuloplasty if required to control the residual insufficiency. Operative mitral valve competence was examined by injecting blood under pressure through the left ventricular apex, because in those early years transesophageal echocardiography was not

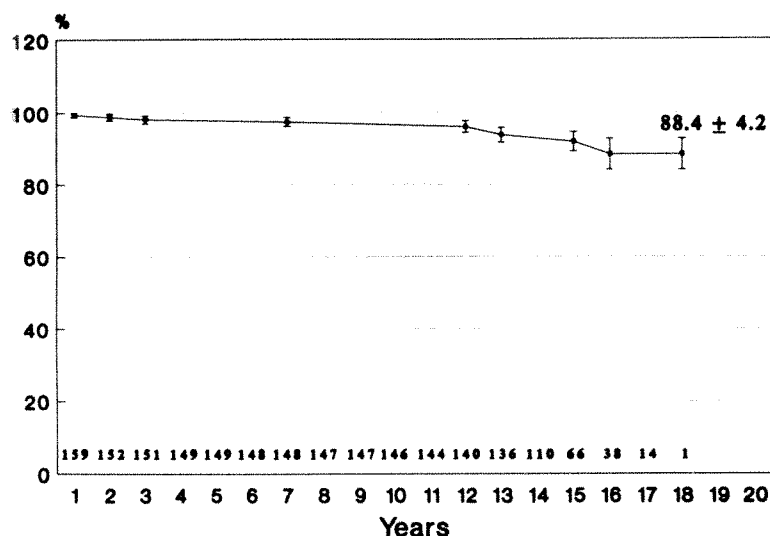
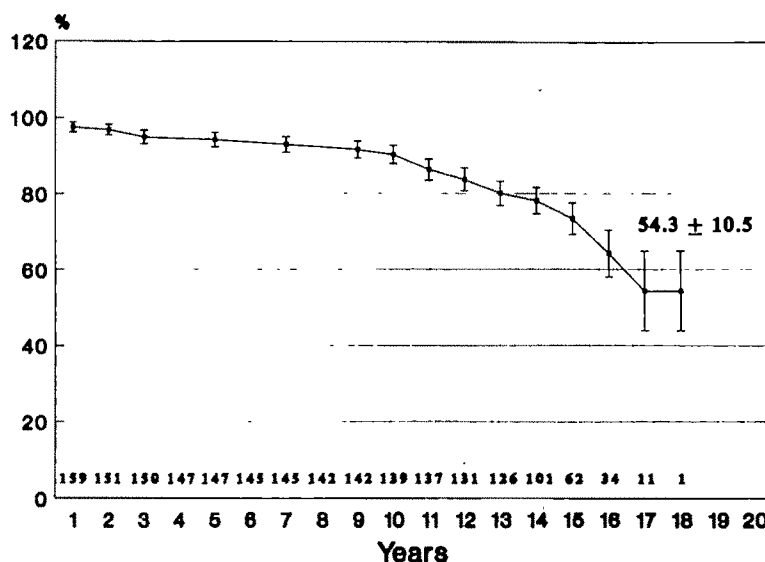


Fig 3. Actuarial curve of freedom from reoperation for any cause.

Fig 4. Event-free actuarial curve at 18-year follow-up.



available. The actuarial survival and freedom from valve-related reoperation at long-term follow-up, and the fact that a majority of patients are leading an active normal life (91.6% in class I or II), are similar to the data reported by other authors [11-13, 16]. We believe that the incidence of restenosis is intimately connected with the fusion of the subvalvular apparatus, so a complete repair is a crucial factor to produce a satisfactory long-term functional outcome.

Open mitral commissurotomy also allows the surgeon to visualize and remove left atrial thrombus, which was found in 13.2% of the patients in close relation to the presence of atrial fibrillation and previous thromboembolic episodes [9].

Statistical analysis of the clinical data has demonstrated that the age at the time of operation and the presence of left atrial thrombus represent risk factors for late mortality. When the incidence of thromboembolic episodes after OMC was studied for the different subgroups of patients, we found that of patients in atrial fibrillation ($n = 66$) only 4 patients (6%) had a thromboembolic event, compared with 11 patients (11.8%) in the group of patients in sinus

rhythm ($n = 93$). This controversial finding was probably due to the fact that most of the patients ($n = 9$) in sinus rhythm had a prosthetic annuloplasty ring to repair the mitral valve at the time of OMC. The presence of this prosthetic material in the left atrium could act as a trigger of thrombus formation. As shown in Table 2, the presence of the annuloplasty ring (10 of 15 patients) increased the incidence of postoperative thromboembolism with a high statistical significance ($p < 0.001$). Thromboembolism occurred in 2 patients (9.5%) with preoperative atrial thrombosis ($n = 21$), compared with 13 patients (9.4%) without atrial thrombosis ($n = 138$; $p > 0.05$).

All patients with preoperative thromboembolism and those with atrial thrombus ($n = 52$) received permanent oral anticoagulant therapy after operation. Six thromboembolic episodes occurred in this group of patients and nine events in the remaining 107 patients (11.5% versus 8.4%; $p > 0.05$).

Presence of localized valve calcification and subvalvular apparatus pathology were not determinant in the long-term results, as the group of patients with unsatisfactory valve anatomy at operation had an outcome similar to that

Table 2. Risk Factors in Open Mitral Commissurotomy

Risk Factor	Death (n = 13)	Reoperation (n = 11)	Thromboembolism (n = 15)
Age (y)	50.4 ^a	39.4	41.6
NYHA class III or IV	10 (76.9%)	6 (54.5%)	10 (66.7%)
Atrial fibrillation	9 (69.2%)	5 (45.4%)	4 (26.7%)
Preoperative thromboembolism	5 (38.5%)	1 (9.1%)	6 (40%)
Pulmonary resistance (dynes · s · cm ⁻⁵)	603	640	476
Atrial thrombosis	5 ^b (38.5%)	1 (9.1%)	2 (13.3%)
Papillotomy (subvalvular disease)	8 (61.5%)	7 (63.6%)	10 (66.7%)
Valvular calcification	1 (7.7%)	1 (9.1%)	2 (13.3%)
Annuloplasty	5 (38.5%)	3 (27.3%)	10 ^a (66.7%)

^a $p < 0.001$. ^b $p < 0.01$.

NYHA = New York Heart Association.

of those who did not. Associated mitral valve surgical repair, particularly in patients with residual incompetence after OMC, was important to assure long-term satisfactory results.

In conclusion, OMC with concomitant mitral valve operation to repair the associated lesions represents a stable and safe surgical treatment with a low hospital and late mortality and a low incidence of long-term valve-related complications requiring reoperation. Most patients are asymptomatic 14 to 18 years after operation, leading an active normal life.

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Pulmonary Artery Size and Clinical Outcome After the Modified Fontan Operation

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The maximum cross-sectional area of the central pulmonary arteries indexed to the body surface area (pulmonary artery index [PAI]) was measured preoperatively from angiograms in 173 patients evaluated for a Fontan-type operation between 1981 and June 1989. Of these, 34 patients underwent another palliative procedure, 8 primarily on the basis of small pulmonary arteries (PAI, 106 to 167 mm²/m²). The mean PAI of this group was significantly smaller than the mean PAI of the remaining 139 patients who underwent a Fontan operation (136 ± 20 versus 310 ± 113 mm²/m²) ($p < 0.001$). The patients who underwent a Fontan operation were evaluated according to three overlapping end points: (1) hospital death or takedown of repair (12.2%), (2) early failure (cumulative death or takedown of repair within 6 months of operation) (16.5%), and (3) early failure or persistent effusions (33.8%). With regard to these end points, no significant difference in pulmonary artery size could be found between patients having a favorable or unfavorable

outcome. However, among a low-risk subset of 30 patients with tricuspid atresia, those with "early failure or persistent effusions" had significantly smaller pulmonary arteries than those with a good outcome (PAI, 185 ± 47 versus 276 ± 83 mm²/m²) ($p < 0.01$). The postoperative transpulmonary gradient of the 8 patients with the smallest pulmonary arteries who underwent a Fontan operation (all PAIs < 170 mm²/m²) was significantly greater than that of the rest of the study group (9.88 ± 2.3 versus 8.13 ± 2.3 mm Hg) ($p < 0.04$). Small pulmonary arteries, in otherwise good-risk patients, are associated with increased risk of "early failure or persistent effusions" after the Fontan operation. The lowest PAI compatible with success remains unknown. To obtain a more comprehensive assessment of a successful outcome, we suggest that evaluation of patients after a Fontan operation include end points other than hospital death.

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Small pulmonary arteries have been considered a contraindication to the Fontan-type operation since the first successful case was reported in 1971 [1]. Subsequently published guidelines for selection criteria have reinforced the belief that for a successful outcome the pulmonary arteries must be of sufficient size to allow unrestricted flow [2, 3]. This has been defined as a McGoon ratio of 1.8 or greater [4], which is equivalent to a pulmonary artery cross-sectional area index (or pulmonary artery index [PAI]) of more than 200 mm²/m² [Kirklin JW; personal communication, Feb 1990].

In recent years, however, surgeons have extended the modified Fontan procedure to patients who do not satisfy the traditional selection criteria with remarkable success [5-8]. This policy has renewed interest in the influence of central pulmonary artery size on clinical outcome after a Fontan operation, and in identifying the smallest pulmonary arteries consistently compatible with a good clinical outcome. From our data with *intraoperative* measurement of pulmonary artery size, Girod and associates [9] reported successful outcome in a patient with a PAI as low as 188 mm²/m². Bridges and colleagues [10], using preop-

erative echocardiographic measurements, recently reported operative survival in patients with a preoperative PAI less than 100 mm²/m², in whom the pulmonary arteries were enlarged at operation.

These reports prompted us to review our data on pulmonary artery size measured and recorded preoperatively since 1981. Our goal was to further define the relationship between pulmonary artery size and clinical outcome including serious nonfatal complications after the modified Fontan operation.

Material and Methods

Study Design

Between 1981 and June 1989, 173 patients in whom both central pulmonary arteries could be accurately measured from preoperative angiographic studies were considered for a Fontan operation at our institution. Thirty-four patients (19.7%) were considered unsuitable for a Fontan procedure, and in most of these an alternative palliative or preparatory procedure was performed. The available data on these patients were reviewed to determine whether pulmonary artery size influenced the decision not to perform a Fontan procedure.

The study group comprises the remaining 139 patients who underwent a modified Fontan operation. Their rele-

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Table 1. Risk Factors for Patients Undergoing the Fontan Operation (n = 139)

Factor	Mean $\pm$ SD or Percentage	Median	Range
Age (y)	11 $\pm$ 7	10	1-42
Previous procedures (No.)	1.5 $\pm$ 1	1	0-6
Mean PA pressure (mm Hg)	20 $\pm$ 10	18	2-73
Q _p /Q _s	1.6 $\pm$ 1.2	1.1	0.2-6
PARI (U $\cdot$ m ²)	2.0 $\pm$ 1.1	1.85	0.2-4.5
VEDP (mm Hg)	14.4 $\pm$ 4.5	14	6-28
Ejection fraction	0.56 $\pm$ 0.10	0.57	0.35-0.82
LPA repair	23% (n = 33)		
RPA repair	17% (n = 24)		
AVV repair	7% (n = 10)		
AVV replacement	2.1% (n = 3)		

AVV = atrioventricular valve; LPA = left pulmonary artery; PA = pulmonary artery; PARI = pulmonary arteriolar resistance index; Q_p/Q_s = pulmonary to systemic shunt; RPA = right pulmonary artery; VEDP = ventricular end-diastolic pressure.

vant data were entered into a single data base, which is summarized in Table 1. These data are not significantly different from those of the remaining 399 patients undergoing a Fontan operation during the same period. There were 85 male and 54 female patients, ranging in age from 1 to 42 years (median, 10 years). The study group was analyzed using three overlapping criteria for a poor clinical result in an attempt to determine whether pulmonary artery size influenced early mortality or morbidity. The patients' records were reviewed in December 1989, at which time 6-month follow-up data were available on all the patients.

From the study group, a low-risk subgroup of patients was identified (n = 30), and the same analyses were done. The criteria for selection were age 4 years or older, pulmonary arteriolar resistance index less than 2.0 U $\cdot$ m², and no significant atrioventricular valve regurgitation. These patients all had tricuspid atresia and physiology generally favorable for a Fontan operation.

The following preoperative risk factors for hospital death/takedown were analyzed: age at operation, ventricular end-diastolic pressure, pulmonary artery pressure, pulmonary arteriolar resistance index, number of previous operations, ventricular ejection fraction, pulmonary artery size, significant AV valve regurgitation, distorted pulmonary arteries, pathological lesion, and postrepair central venous pressure.

Definitions of Outcome

Hospital death or takedown is defined as death or takedown of the Fontan repair within 30 days of operation or before discharge from hospital. *Early failure* is defined as the cumulative incidence of mortality and takedown of the repair within 6 months (180 days) of operation (including hospital death or takedown). *Failure/effusions* is defined as the cumulative incidence of mortality and takedown of repair within 6 months of operation or prolonged pericardial/pleural effusions, ie, effusions persisting 18 or more

days during the postoperative period or requiring a pericardiectomy or pleurodesis within 6 months of the Fontan operation.

Measurement of Pulmonary Artery Size

All pulmonary angiograms were interpreted at the time of the preoperative evaluation by one cardiac radiologist (P.R.J.). Both pulmonary arteries were measured at the upper lobe bifurcations during that phase of the cardiac cycle associated with maximum size. (This differs slightly from the technique described by Nakata and associates [11], who defined pulmonary artery size in terms of the average of the measurements made during systole and diastole.) The measured diameters of the pulmonary arteries were corrected for magnification, and the cross-sectional areas were calculated from the corrected pulmonary artery diameter size; the areas were summed and divided by the patient's body surface area to yield the PAI, which is expressed as square millimeters per square meter.

Surgical Technique

Our surgical technique reflects the experience obtained in the 703 Fontan operations performed at this institution between October 1973 and December 1989 [12]. Operations were usually performed under deep hypothermia (20° to 25°C) facilitated by periods of low-flow perfusion (0.5 to 1.5 L $\cdot$ min⁻¹ $\cdot$ m⁻²) or circulatory arrest as necessary. Myocardial protection was achieved with intermittent cold blood or crystalloid cardioplegia and topical hypothermia. Direct atriopulmonary connection has remained the preferred anastomosis for tricuspid atresia and double-inlet left ventricle. In most patients with univentricular heart, the systemic and pulmonary venous drainage were partitioned in such a way that the coronary sinus drained into the pulmonary venous side of the atrial baffle, but no special techniques were employed to achieve this if the anatomy was unfavorable.

Perioperative Management

Intraoperatively the patients were well transfused and usually left the operating room with a central venous pressure around 16 to 18 mm Hg. Dopamine and sodium nitroprusside were commenced in dosages of 4 μ g $\cdot$ kg⁻¹ $\cdot$ min⁻¹ and 1 μ g $\cdot$ kg⁻¹ $\cdot$ min⁻¹, respectively, just before weaning from cardiopulmonary bypass, and this ratio was generally maintained in the early postoperative period. During the first 2 days after operation, chest tube drainage was replaced with colloid solutions, blood, or both to maintain an adequate cardiac output with correspondingly less inotropic support.

Mechanical ventilation was continued for an average of 3 to 4 days postoperatively, and no attempt was made to withdraw respiratory support until the patients' hemodynamic and respiratory parameters were stable. Positive end-expiratory pressure of 3 to 5 mm Hg was maintained while the patients were on the ventilator, with the head of the bed elevated about 10 to 15 degrees.

Because transient venous congestion of the viscera often delayed the return of intestinal function [13], we

frequently initiated parenteral alimentation early postoperatively and continued this until the patient was taking adequate nutrition by mouth.

Methods of Analysis

Wilcoxon rank-sum analysis was used to compare continuous variables. All *t* tests are two-tailed, and a *p* value of 0.05 or less was considered significant. Discrete variables were analyzed with χ^2 tables using Yates' correction. Data are represented as mean $\pm$ standard deviation, followed by the median value in parenthesis where applicable.

Results

Influence of Pulmonary Artery Size on Patient Selection

Of the 173 patients who were evaluated for a Fontan procedure, 34 were considered unsuitable for this operation; in 8 of these patients the decision not to perform a Fontan-type operation was made predominantly on the basis of small pulmonary artery size. Their PAIs ranged from 106 to 167 mm²/m², and their mean PAI was significantly smaller than that of the 139 patients who underwent a Fontan operation: 136 $\pm$ 20 versus 310 $\pm$ 113 mm²/m² (*p* < 0.001). The subjective preoperative evaluation was that the pulmonary arteries were too small for a Fontan operation.

In retrospect, however, 8 patients with pulmonary artery indices in the same range did undergo a Fontan operation (PAI = 108, 116, 139, 140, 145, 150, 158, and 168 mm²/m²). In 2, pulmonary artery augmentation was indeed extended beyond the bifurcation, ie, the point of measurement of the PAI. With one exception, these were all considered to be "low-risk" candidates except for their small pulmonary arteries: 6 had tricuspid atresia, 1 had double-inlet left ventricle, and 1 had mitral atresia. The patient with mitral atresia and the smallest PAI (108 mm²/m²) died 4 years after his modified Fontan operation while awaiting heart transplantation after eventual takedown of his Fontan repair. In the interim he had undergone reconstruction of the right pulmonary artery and systemic atrioventricular valve replacement, and a pulmonary angiogram shortly before his death (Fig 1) demonstrated that the pulmonary arteries had not grown significantly since his first operation (PAI, 108 mm²/m² versus 107 mm²/m²). The other 7 patients were all alive and well at last follow-up 8 months and 2, 4, 5, 5, 6, and 8 years after operation, although 3 had persistent effusions and 3 had low cardiac output in the early postoperative period. The mean transpulmonary gradient (central venous pressure - left atrial pressure), measured at the end of the operation of these 8 patients, was significantly higher (9.88 $\pm$ 2.3 mm Hg; median, 11 mm Hg) than that of the rest of the patients who underwent a Fontan operation (8.13 $\pm$ 2.3 mm Hg; median, 8 mm Hg) (*p* < 0.04). The highest preoperatively measured pulmonary arteriolar resistance index among these 8 patients was 2.4 U $\cdot$ m²; 5 of the 8 patients are included among the low-risk subgroup of tricuspid atresia patients.

There was no significant difference in preoperative PAI between those who did and did not have pulmonary

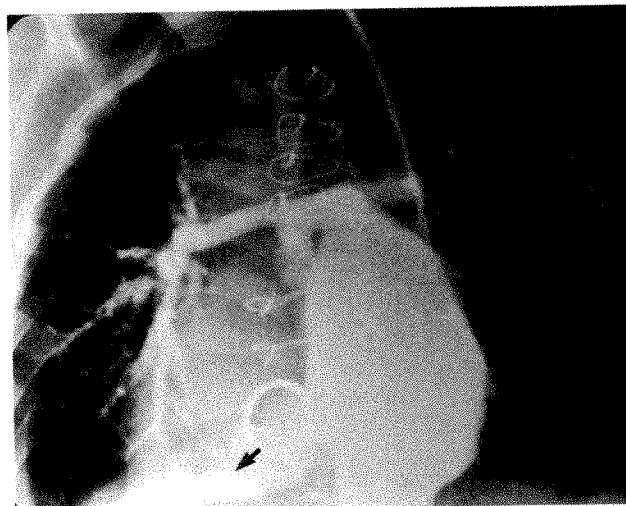


Fig 1. Angiogram obtained 5 days before takedown of the modified Fontan repair. Note the small pulmonary arteries, which preoperatively were estimated to have a pulmonary artery index of 108 mm²/m². Note the left-sided morphologically right atrium, and the prosthetic atrioventricular valve. Arrow indicates the small interatrial right-to-left shunt demonstrated by contrast material entering the pulmonary venous atrium from the dilated systemic venous atrium.

artery augmentation at the time of their operation. This similarity in preoperative PAI (Fig 2) suggests that the measurements were generally made beyond the point of the reconstruction, and that the PAIs were not augmented by the procedure. If the PAIs were clearly smaller in the patients in whom pulmonary artery reconstruction was done, then it might well be argued that the PAI measurements were not made distal to the most distal point of repair. Although generally true, this inference is inaccurate in at least 2 patients with small pulmonary arteries in whom the reconstruction extended beyond the bifurcation.

Clinical Outcome According to Defined End Points

The hospital mortality for the study group (*n* = 139) was 11.6%, which includes 3 patients who did not survive

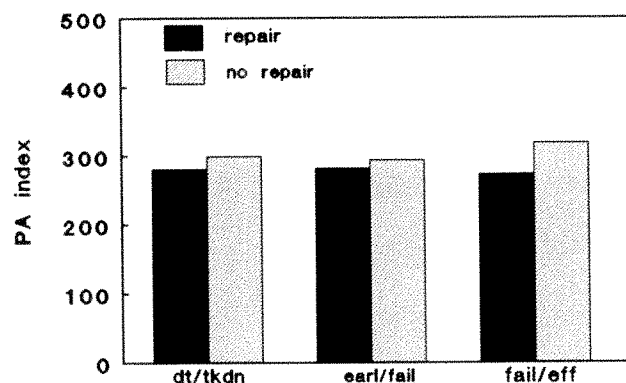


Fig 2. Comparison of preoperative pulmonary artery (PA) index according to outcome in patients with and without pulmonary artery reconstruction. (dt/tkdn = death/takedown; earl/fail = early failure; fail/eff = early failure or persistent effusions.)

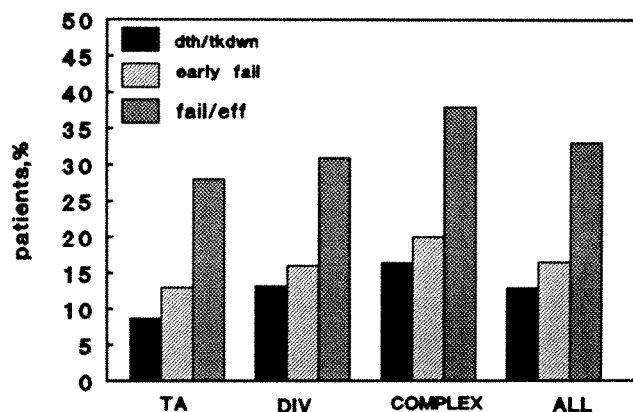


Fig 3. Results of Fontan operation in patients with tricuspid atresia (TA) ($n = 46$), double-inlet ventricle (DIV) ($n = 38$), complex pathology ($n = 55$), and as a single group (ALL) ($n = 139$) according to three end points: death/takedown (dth/tkdown), early failure (early fail), and early failure or persistent effusions (fail/eff).

takedown of their repair. One additional patient is alive after early takedown of his Fontan anastomosis, yielding a combined incidence of hospital mortality and takedown of 12.2%. Early failure (cumulative 6-month mortality and takedown incidence) was 16.5%. In addition, 17.3% of patients had prolonged effusions according to our definition. The combined failure/effusion rate was therefore 33.8% ($16.5\% \pm 17.3\%$). Separated into previously defined pathological groups, the results are summarized in Figure 3.

Of the risk factors for hospital death/takedown that were analyzed univariately, only early age ($p < 0.01$), increased pulmonary arteriolar resistance index ($p < 0.05$), and postrepair central venous pressure greater than 20 mm Hg ($p < 0.02$) reached significance. In this series neither pathological lesion nor pulmonary artery size was a significant risk factor for hospital mortality or takedown. Most patients, however, had multiple risk factors, making interpretation of the data difficult (see Table 1); in this regard, only 4 patients satisfied all 10 of the initial selection criteria [3]. Nonoverlapping missing data precluded any meaningful multivariate analysis of risk factors for death or takedown.

The distribution of PAIs among all patients having a "good outcome" after the Fontan operation varied widely from relatively small ($108 \text{ mm}^2/\text{m}^2$) to very large ($>550 \text{ mm}^2/\text{m}^2$). Although there was considerable overlap, the distribution of PAIs by intervals for all three "poor-outcome" end points was skewed to the left (Fig 4), suggesting that patients with smaller PAIs generally fared less well than patients with larger PAIs.

Outcome in Low-Risk Patients

Using our analyses and other published risk factors for hospital mortality [3, 4, 5, 7, 12, 14-16] we identified a low-risk subset of patients with tricuspid atresia. All patients in this subset satisfied at least three of ten of the original selection criteria [3]. By analyzing this low-risk subset of patients, we attempted to more clearly establish

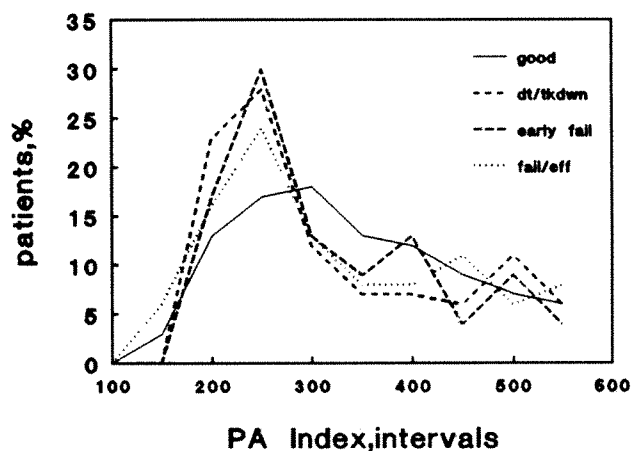


Fig 4. Relationship of pulmonary artery (PA) index to defined end points by intervals for study group ($n = 139$). (dt/tkdown = death/takedown; early fail = early failure; fail/eff = early failure or persistent effusions.)

whether central pulmonary artery size in any way influenced their clinical outcome in terms of increased morbidity or mortality.

Within this subset ($n = 30$) the incidence of death/takedown was 3.3%, early failure occurred in 6.6%, and failure/effusions was identified in 20%, compared with 15.6%, 19.3%, and 37.6%, respectively, for the rest of the study group. Within this subgroup, the pulmonary artery size of those patients having failure/effusions was $185 \pm 47 \text{ mm}^2/\text{m}^2$ compared with $276 \pm 82 \text{ mm}^2/\text{m}^2$ in those having a good result ($p < 0.01$) (Fig 5). Furthermore, patients with a PAI less than $250 \text{ mm}^2/\text{m}^2$ had a failure/effusion rate of 43%, whereas those with larger pulmonary arteries without exception all survived with an uncomplicated postoperative course in terms of persistent or recurrent pleural and pericardial effusions ($p < 0.01$). The only patient who died in the hospital had a PAI of $210 \text{ mm}^2/\text{m}^2$, and the only other patient who died within 6 months of operation had a PAI of $198 \text{ mm}^2/\text{m}^2$.

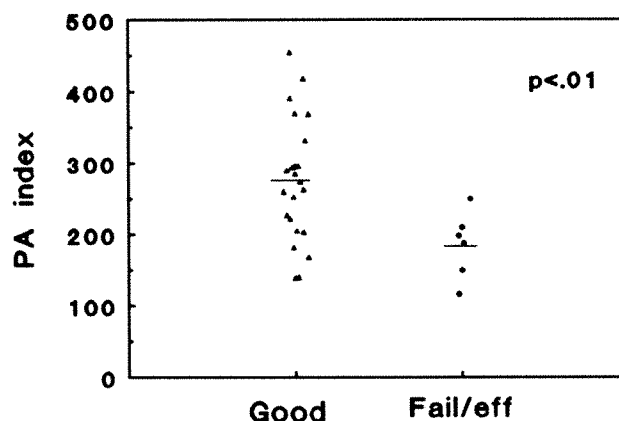


Fig 5. Scatter graph illustrating relationship of pulmonary artery (PA) index to outcome in low-risk patients with tricuspid atresia. Fail/eff represents early failure or persistent effusions.

Comment

End Points

Traditionally hospital discharge has been the end point selected to reflect early outcome after cardiac surgical procedures. We have been concerned, however, that this may not adequately reflect success after the Fontan procedure, as a small proportion of patients who survive their initial hospitalization period die within a few months or suffer debilitating complications of fluid retention, often requiring repeated admissions for pleuropericardial effusions or ascites. To address this aspect we defined the end points early failure and failure/effusions. Use of the 6-month postoperative interval for assessing early failure is supported by the collective experience of Fontan and Kirklin [14, 15], who noted that the early-phase hazard function for mortality after the Fontan procedure greatly diminishes after this interval.

The period of 18 days or more that was considered excessive for postoperative effusions was arbitrarily selected before the data were collected and the analyses done.

Overall Results

Patients referred for consideration of a Fontan procedure have already been preselected by their referring physicians on the basis of established selection criteria. Despite this bias, 19.7% of our referrals were thought unsuitable for a Fontan-type repair, and about a quarter of these were disqualified primarily on the basis of pulmonary artery anatomy. The central pulmonary arteries of these patients were clearly smaller than the average of those who underwent a Fontan operation; however, an equal number of patients with similarly small pulmonary arteries (PAI range, 110 to 170 mm²/m²) were accepted for a one-ventricle repair, and all survived the first 6 months after operation. Their postoperative courses were generally more stormy though, and of the 8 patients 3 had low cardiac output needing prolonged inotropic support postoperatively and 3 had prolonged pleural effusions (up to 43 days postoperatively). With one exception (a patient with mitral atresia and a PAI of 108 mm²/m² who died 4 years later despite repeated operation in the interim), all these patients had less complex anatomy (6 had tricuspid atresia, 1 had double-inlet left ventricle), and 5 were identified as low-risk patients in terms of our study design. The transpulmonary gradients in these patients were also significantly greater than the rest of the study group, and smaller pulmonary artery size probably influenced these circumstances.

When we analyzed the 139 patients in the study group who underwent a Fontan procedure, we could find no statistically significant influence exercised by pulmonary artery size according to the end points defined (see Fig 4). This may reflect the complexity of this patient population rather than a relative lack of significance of pulmonary artery size [4, 13, 17, 18]; in the low-risk subset of patients with tricuspid atresia, smaller pulmonary arteries were clearly associated with a higher probability of failure/effusions ($p < 0.01$) (see Fig 5). A PAI less than 250

mm²/m² was able to predict this end point with reasonable accuracy ($p < 0.01$), supporting the similar findings of others [4, 11]. In this instance failure/effusions reflects predominantly increased morbidity in the form of persistent or recurrent effusions (4 of the 6 patients), although the 2 patients in this low-risk group ($n = 30$) who died within 6 months of their operation both had PAIs less than 250 mm²/m² (198 and 210 mm²/m²).

Although it is clear that the major area of resistance to flow across the pulmonary bed is at the arteriolar level [19], small pulmonary arteries also contribute to this resistance. This has been established in complete repair of tetralogy of Fallot with hypoplastic pulmonary arteries [19, 20], in which correction has been advised only if the Nakata pulmonary artery index exceeds 100 mm²/m² [11]. It is unlikely, therefore, that a Fontan operation, in which there is no ventricle driving the pulmonary circulation, can succeed in the presence of pulmonary arteries that have a PAI of 100 mm²/m² or less, equivalent to a McGoon ratio of 1.2 [Kirklin JW; personal communication, Feb 1990]. The preoperative echocardiographic data of Bridges and associates [10], indicating success with the Fontan procedure in a patient with a PAI of 48 mm²/m², were not supported by similar intraoperative or postoperative measurements, and pulmonary artery augmentation probably contributed significantly to the postoperative size of the pulmonary arteries. When pulmonary artery augmentation accompanies the Fontan operation, the validity of the preoperative measurement depends on the site that the measurements are made, ie, the measurement should be made distal to the site of expected augmentation. For this, it may be necessary to measure the branch pulmonary arteries rather than the distal pulmonary arteries. Similarly, a comparison of preoperative data and intraoperative measurements may not be valid, as the former may underestimate the pulmonary artery size, particularly if the pulmonary blood flow is reduced [21]. Hence relating the observations in this study to our previously published intraoperative data [9] may be misleading.

Data from this analysis support the data of Fontan and associates [4] and others [11, 17, 18] that small preoperative pulmonary artery size is associated with a higher mortality and morbidity after the Fontan operation in low-risk patients, even though individual predictions cannot be made. Although many otherwise low-risk patients with PAIs in the range 120 to 170 mm²/m² may receive acceptable palliation from their Fontan operation in the short term, as evident from this study, we remain reluctant to perform a Fontan operation in general if the PAI is less than 170 to 180 mm²/m². In these circumstances we still prefer to encourage growth of the pulmonary arteries by constructing a generous central shunt, and reevaluate the patient 6 months to a year later.

We wish to thank Mr Duane M. Ilstrup from the Section of Biostatistics for his advice in the preparation of the statistical analyses.

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Platelet Function in Cardiac Surgery: Influence of Temperature and Aprotinin

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Hypothermic cardiopulmonary bypass (CPB) has been associated with both coagulation defects and hemorrhage. The influence of temperature on platelet function and the benefits of aprotinin in this situation were studied in 60 patients undergoing elective aortocoronary bypass grafting. The patients were randomly divided into four groups (15 patients per group): group 1, normothermic CPB (nasopharyngeal temperature $> 34^{\circ}\text{C}$); group 2, normothermic bypass and administration of high-dose aprotinin (2 million IU before CPB, 500,000 IU/h until the end of the operation, and 2 million IU added to the prime); group 3, hypothermic CPB (nasopharyngeal temperature $< 28^{\circ}\text{C}$); and group 4, hypothermic CPB and aprotinin. Platelet function was evaluated by aggregometry (turbidimetric technique), and aggregation was induced by adenosine diphosphate (1 and 2 $\mu\text{mol/L}$), collagen (4 $\mu\text{g/L}$), and epinephrine (25 $\mu\text{mol/L}$) before, during, and after CPB into the first postoperative day. Starting from comparable baseline values, maximum platelet aggregation and maximum gradient of platelet aggregation were significantly most reduced af-

ter CPB in group 3 (hypothermic CPB without aprotinin) (ranging from -30% to -53% relative to baseline values). In comparison with the other groups, platelet function in this group also recovered less quickly in the later postbypass period. Hypothermic CPB with aprotinin resulted in less-altered platelet function than hypothermic CPB without aprotinin. Platelet aggregation in aprotinin-treated patients was comparable overall with that in patients undergoing normothermic CPB. On the first postoperative day, aggregation variables had returned to or exceeded baseline values. Blood loss on the first postoperative day was significantly higher in group 3 ($680 \pm 220 \text{ mL}$) than in the other groups, and need for homologous blood and fresh frozen plasma was also most pronounced in these patients (6 units of packed red cells and 4 units of fresh frozen plasma). We conclude that aprotinin blunted the negative effects of hypothermic CPB on platelet function but failed to have any beneficial effects in patients undergoing normothermic CPB.

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Approximately 10% to 20% of patients undergoing cardiac surgical procedures exhibit inadequate hemostasis, which varies in duration and severity. These patients often require treatment with homologous blood or blood products [1], and approximately 3% will need reexploration [2]. Therefore, various pharmacological and nonpharmacological interventions to reduce blood loss and need for homologous blood have been used, including asanguineous prime, predonation of autologous blood, and blood salvaging systems such as the Cell Saver (Haemonetics, Braintree, MA) or hemofiltration devices [3, 4]. In recent years, interest has focused on pharmacological manipulations to achieve hemostasis [5, 6]. The proteinase inhibitor aprotinin appears the most promising; several studies [7-10] have reported beneficial effects of aprotinin on reducing blood loss and homologous blood requirements.

Defects in platelet function are considered very important in postbypass hemorrhage [11-14]. Factors that con-

tribute to acquired platelet abnormalities include shear stress, blood gas interaction, heparin sodium and protamine sulfate, and interaction of platelets with the non-endothelial surfaces of the cardiopulmonary bypass (CPB) system [15]. Moreover, it is well established that platelet dysfunction can be induced by hypothermia [16]. Temperature-dependent morphological alterations include changes in the platelet membrane and its function [17].

The aim of this study was to investigate the influence of hypothermic CPB on platelet function and the possible benefits of high-dose aprotinin in patients undergoing a cardiac operation.

Material and Methods

Sixty consecutive male patients scheduled for elective aortocoronary bypass grafting were studied. Informed consent was obtained from all patients according to the protocol of the ethic study committee of the hospital. In all patients, a left internal mammary artery graft was used in addition to saphenous vein grafting. Inclusion criteria were disease of four or more vessels and an expected bypass time of longer than 80 minutes. Exclusion criteria were preoperative coagulation disorders, concomitant

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valvular diseases, and medication with aspirin or other cyclooxygenase inhibitors within the last 10 days before operation.

The patients who met the criteria were prospectively randomized into four groups (15 patients per group):

Group 1: normothermic CPB (nasopharyngeal temperature $> 34^{\circ}\text{C}$)

Group 2: normothermic CPB and administration of high-dose aprotinin (2 million IU after induction of anesthesia, 500,000 IU/h until the end of the operation, and 2 million IU added to the prime)

Group 3: hypothermic CPB (nasopharyngeal temperature $< 28^{\circ}\text{C}$)

Group 4: hypothermic CPB and aprotinin

Anesthesia and Cardiopulmonary Bypass

Induction and maintenance of anesthesia were comparable for all groups and consisted of weight-related doses of fentanyl, pancuronium bromide, and midazolam hydrochloride. The patients remained on controlled mechanical ventilation for at least 5 hours after the operation.

Five minutes before initiation of CPB, 300 IU/kg of bovine lung heparin was administered to achieve anticoagulation. Bypass was carried out with a nonpulsatile pump and a membrane oxygenator (Sorin 41; Sorin, Torino, Italy). The circuit was primed with 1,000 mL of Ringer's solution, 1,000 mL of dextrose (5%), and 250 mL of human albumin (5%) in all groups as well as aprotinin in groups 2 and 4. In all groups, a perfusion flow of $2.4 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ was maintained for the entire bypass period. Blood was returned to the circuit using a two-stage cannula (monoatrial cannulation technique). For myocardial preservation, 1,000 mL of cardioplegic solution (Bretschneider) was infused.

Within 20 minutes after the start of CPB, the blood in the circuit was concentrated by a hemofiltration device (HF-80; Fresenius, Bad Homburg, Germany) to adjust the hemoglobin level between 80 and 90 g/L (8 and 9 g/dL) (hematocrit, 0.22 to 0.25). Later during CPB, Ringer's solution was added to the circuit when the hemoglobin level was greater than 70 g/L (7 g/dL) (hematocrit < 0.20); packed red cells were given when the hemoglobin level was lower. Patients in groups 2 and 4 were cooled by both surface cooling and the CPB system. Esophageal temperature, rectal temperature, and blood temperature in the oxygenator were measured continuously.

During weaning from CPB, as much pump blood was infused as necessary to keep the pulmonary capillary wedge pressure between 10 and 12 mm Hg. After weaning from CPB was completed, the residual blood in the circuit was salvaged by the hemofiltration device, and this autologous blood was retransfused until the end of the operation. Protamine sulfate was given in the same dose as the initial heparin dose to reverse the heparin effects. All patients were operated on by the same surgical team, which was blinded to the groups.

Data Points and Measured Variables

Arterial blood samples were taken after induction of anesthesia (baseline values), 20 minutes after the start of

CPB (after completion of hemoconcentration by hemofiltration), after weaning from bypass (before injection of protamine), at the end of the operation, 5 hours after the end of the operation, and on the morning of the first postoperative day.

Platelet aggregation was studied using the turbidimetric method [18] and a double-channel APACT aggregometer (Labor, Ahrensburg, Germany). Before aggregometry, platelet count was adjusted to approximately $150 \times 10^9/\text{L}$ ($150,000/\mu\text{L}$). Platelet aggregation was induced by adenosine diphosphate (1.0 and $2.0 \mu\text{mol/L}$), collagen ($4 \mu\text{g/mL}$), epinephrine ($25 \mu\text{mol/L}$), and NaCl (control). The maximum increase in light transmission after addition of the aggregating agent was defined as maximum platelet aggregation (percent increase). The maximum increase per minute was defined as maximum gradient of platelet aggregation (percent increase per minute). All measurements were carried out in duplicate. In addition, hemoglobin, hematocrit, platelet count, and activated clotting time were measured.

To maintain stable hemodynamics, albumin (5%) was given postoperatively (when pulmonary capillary wedge pressure was lower than 7 mm Hg and cardiac index was less than $2.30 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$). Packed red cells were given when the hemoglobin level was less than 90 g/L (9 g/dL) (hematocrit < 0.25). All volume therapy was indicated by anesthesiologists and intensivists who were not involved in the study and were blinded to the patient groups. Blood loss was calculated from intraoperative suction and chest tube drainage in the intensive care unit. Use of homologous blood and blood products (platelets or fresh frozen plasma) was also documented.

Statistical Analysis

Power analysis was carried out before starting the study to determine the number of patients necessary to protect from type II errors in the statistical interpretation. The mean $\pm$ the standard deviation was calculated for each variable. For statistical interpretation, one- and two-factor analyses of variance (including multivariate analysis of variance and the Scheffé test) were used. Percent changes from baseline were calculated for all aggregation variables. The χ^2 test was used to analyze differences in homologous blood use. A p value of less than 0.05 was considered significant.

Results

Biometric data and CPB data were comparable for the four groups (Table 1). Fluid balance during CPB (input and output) was significantly higher in the two groups undergoing hypothermic CPB than in the normothermic CPB groups. Blood loss was significantly highest in group 3 (hypothermia without aprotinin) (Fig 1), and the need for homologous blood (6 units of packed red cells) and blood derivatives (4 units of fresh frozen plasma) was also highest in these patients (see Table 1).

The degree of hemodilution (hematocrit) and the platelet count did not differ between groups during the entire study period (Table 2).

Table 1. Biometric and Cardiopulmonary Bypass Data^a

Variable	Normothermia	Normothermia + Aprotinin	Hypothermia	Hypothermia + Aprotinin
Age (y)	61.5 ± 6.0	63.5 ± 8.8	62.4 ± 5.0	64.1 ± 7.1
Weight (kg)	77.5 ± 8.7	78.2 ± 10.1	79.4 ± 9.6	78.3 ± 11.1
CPB (min)	99.6 ± 20.1	96.8 ± 27.1	103.1 ± 25.5	107.1 ± 20.9
Aortic cross-clamping (min)	58.6 ± 16.7	59.1 ± 17.1	63.2 ± 15.8	65.2 ± 16.2
Fluid balance during CPB (mL)	+670 ± 350	+420 ± 380	+1,120 ± 610 ^b	+1,020 ± 660 ^b
Lowest temperature (°C)				
Rectal	35.0 ± 0.4	34.8 ± 0.4	27.2 ± 0.3	27.1 ± 0.5
Nasopharyngeal	34.9 ± 0.2	34.7 ± 0.2	25.3 ± 1.0	25.7 ± 1.4
Oxygenator	34.0 ± 0.4	34.3 ± 0.6	21.1 ± 0.9	22.2 ± 0.9
Homologous blood (U)				
PRC	2	3	6 ^b	2
FFP	0	0	4 ^b	0

^a Where applicable, data are shown as the mean ± the standard deviation.^b Significance: $p < 0.05$ compared with the other groups.

CPB = cardiopulmonary bypass; FFP = fresh frozen plasma; PRC = packed red cells.

At baseline, all aggregation variables were comparable in the four groups (Figs 2-5). Cardiopulmonary bypass resulted in reduced maximum platelet aggregation and maximum gradient of platelet aggregation for all inducers. Aprotinin was without beneficial effect on platelet aggregometry in patients having normothermic CPB. Overall, alterations in platelet aggregometry were significantly most pronounced in the patients undergoing hypothermic CPB without aprotinin (group 3) (ranging from -30% to -53% relative to baseline values). When hypothermia was used in combination with aprotinin (group 4), aggregation was significantly less compromised than in group 3. Both maximum platelet aggregation and maximum gradient of platelet aggregation recovered more slowly in group 3 (hypothermia without aprotinin) than in the other groups and showed significant differences with them as late as 5 hours after operation. On the first postoperative day, all aggregation variables had returned

to or exceeded baseline values (ranging from +2% to +28% relative to baseline values).

None of the patients sustained sequelae after the study. All patients were discharged from the intensive care unit on the third postoperative day at the latest.

Comment

During CPB, contact between blood and nonphysiological surfaces affects both cellular and noncellular constituents [13, 15]. Platelets are altered during bypass in many ways. Activation of platelets by CPB leads to decreased adhesiveness, reduced membrane binding of fibrinogen, alpha granule release, and a reduced in vitro response to adenosine diphosphate and collagen [12-14, 19, 20]. The precise defects responsible for platelet dysfunction secondary to CPB are controversial. Hypothermia is reported to be one important factor by which platelet function can be significantly altered [21-24]. Lu and colleagues [25] demonstrated that lowering the incubation temperature from 37° to 22°C results in an increase in the expression of fibrinogen receptors, platelet release, and platelet aggregation.

In the present study, aggregometry was used because it is reported to be an established technique for evaluating platelet function in cardiac surgery [12, 13, 19]. Like others [26], we found a reduced platelet aggregability in all patients after CPB. Friedenbergs and associates [26] demonstrated abnormalities in aggregation with all three inducers—epinephrine, collagen, and adenosine diphosphate—in patients undergoing CPB: the second phase of platelet aggregation with epinephrine was abolished, the response to collagen was delayed and attenuated, and the response to adenosine diphosphate was attenuated with early disaggregation. In the present study, not only were alterations in platelet function most pronounced in patients who underwent hypothermic CPB without aprotinin (group 3), but also recovery of platelet function in the later postbypass period occurred more slowly compared with the other groups. Moreover, postoperative blood

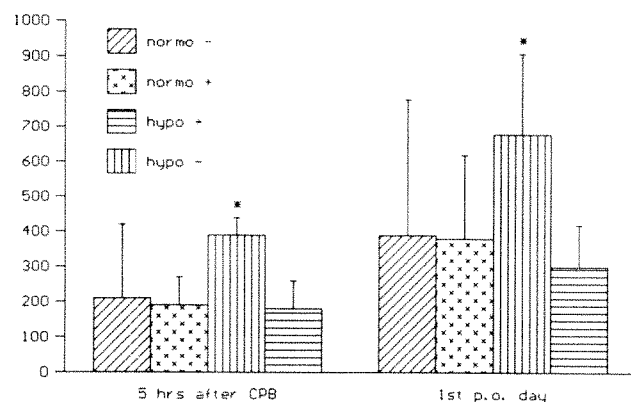


Fig 1. Postoperative blood loss (in milliliters) in the four groups. (CPB = cardiopulmonary bypass; hypo+ = hypothermia with aprotinin [group 4]; hypo- = hypothermia alone [group 3]; normo+ = normothermia with aprotinin [group 2]; normo- = normothermic alone [group 1]; p.o. = postoperative; * = $p < 0.05$ compared with other groups.)

Table 2. Platelet Count and Hematocrit^a

Variable	After Induction	20 Minutes of CPB	After CPB	End of Operation	5 Hours Postop	Post Day 1
Platelet count (10 ⁹ /L)						
Normothermia	178 ± 24	142 ± 22	160 ± 32	160 ± 34	177 ± 23	165 ± 34
Normothermia + aprotinin	170 ± 29	146 ± 22	161 ± 30	155 ± 29	159 ± 25	163 ± 30
Hypothermia	169 ± 26	126 ± 21	147 ± 29	150 ± 29	151 ± 29	156 ± 29
Hypothermia + aprotinin	168 ± 23	125 ± 17	150 ± 25	152 ± 34	159 ± 20	170 ± 36
Hematocrit						
Normothermia	0.38 ± 0.02	0.23 ± 0.03	0.26 ± 0.02	0.30 ± 0.02	0.36 ± 0.02	0.35 ± 0.02
Normothermia + aprotinin	0.37 ± 0.03	0.25 ± 0.03	0.27 ± 0.02	0.31 ± 0.02	0.37 ± 0.02	0.36 ± 0.03
Hypothermia	0.37 ± 0.03	0.25 ± 0.02	0.27 ± 0.03	0.31 ± 0.03	0.36 ± 0.04	0.34 ± 0.03
Hypothermia + aprotinin	0.36 ± 0.02	0.25 ± 0.02	0.27 ± 0.03	0.32 ± 0.02	0.37 ± 0.03	0.37 ± 0.03

^a Data are shown as the mean ± the standard deviation.

CPB = cardiopulmonary bypass.

loss and need for homologous blood and blood products were highest in group 3, indicating the negative influence of hypothermia during CPB on hemostasis, including platelet function.

In several studies [7-10], aprotinin was demonstrated to be the most promising pharmacological intervention to

improve hemostasis and reduce blood loss in cardiac surgery, and routine use of aprotinin was reported to be a safe measure to make cardiac operations "drier." The properties causing the beneficial effect of aprotinin are controversial [27]. However, direct (by stabilization of platelet membrane receptors) or indirect (by its antifibri-

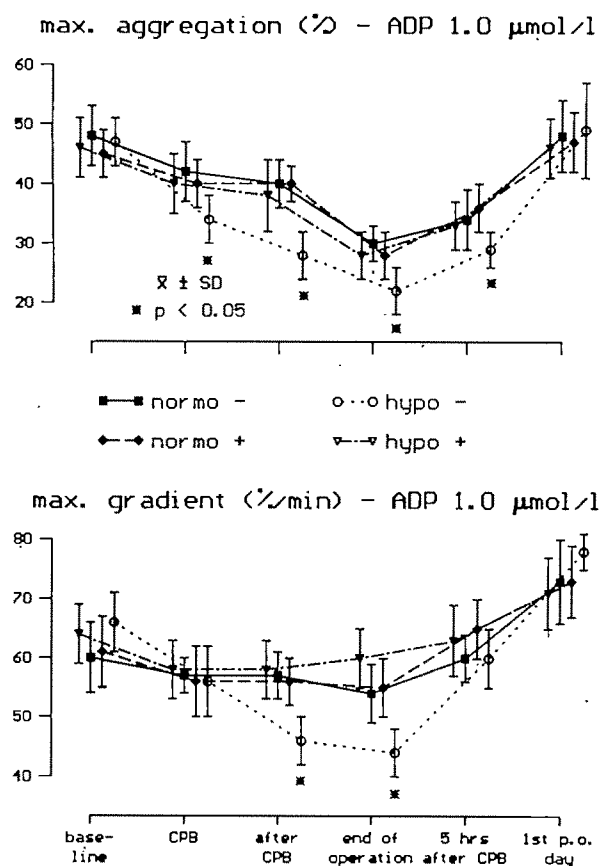


Fig 2. Changes in maximum (max.) platelet aggregation and maximum gradient of platelet aggregation induced by adenosine diphosphate (ADP) (1.0 µmol/L) compared with preoperative control. (SD = standard deviation; $\bar{x}$ = mean; other abbreviations are the same as in Figure 1.)

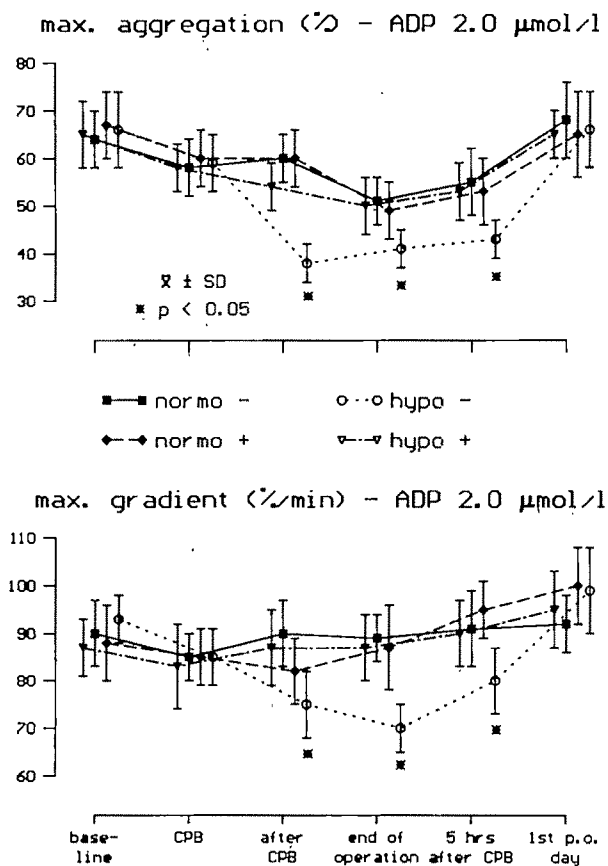


Fig 3. Changes in maximum (max.) platelet aggregation and maximum gradient of platelet aggregation induced by adenosine diphosphate (ADP) (2.0 µmol/L) compared with preoperative control. (SD = standard deviation; $\bar{x}$ = mean; other abbreviations are the same as in Figure 1.)

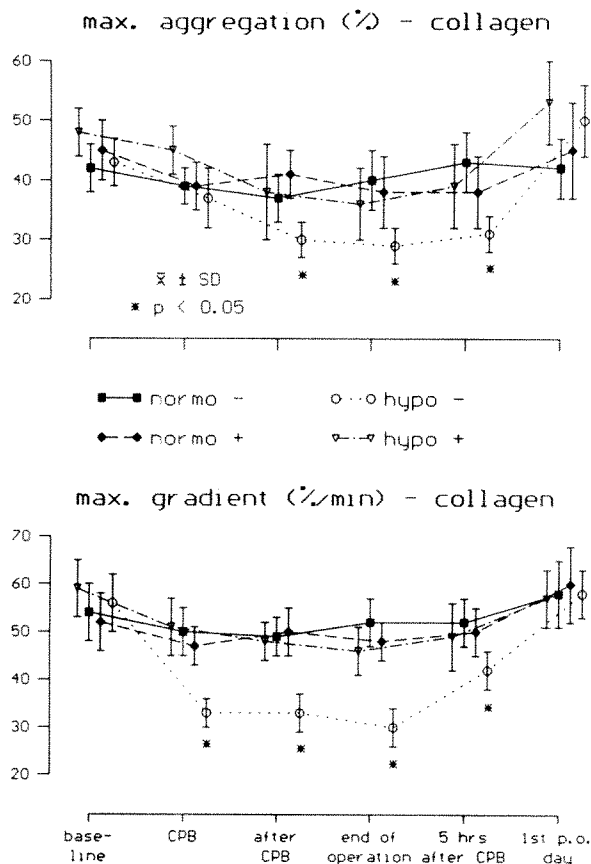


Fig 4. Changes in maximum (max.) platelet aggregation and maximum gradient of platelet aggregation induced by collagen (4 μ g/L) compared with preoperative control. (SD = standard deviation; $\bar{x}$ = mean; other abbreviations are the same as in Figure 1.)

nolytic action) preservation of platelets was shown to be one of the major actions of this substance [28–30]. The use of aprotinin resulted in inhibition of the plasmin-related degradation of GP 1b receptor in platelets [29]. Thus, the antifibrinolytic properties of aprotinin may affect platelets in this way [31].

Some studies reported increased fibrinolytic activity during CPB with a resulting increase in fibrin degradation products. Fibrin degradation products appear to interfere with platelet function [32]. Bick [23], however, demonstrated that there is a poor correlation between levels of circulating fibrin degradation products and the degree of abnormal platelet function during CPB. Also, in a recent study by Marx and colleagues [31], aprotinin failed to cause any relevant inhibition of platelet stimulation during cardiac operations. These results are in accordance with those of the present study, in which platelet aggregation in aprotinin-treated and nontreated *normothermic* patients was without significant differences. Postoperative blood loss and the need for homologous blood were also comparable in these two groups.

However, a definitely positive effect of aprotinin was noticeable when hypothermia was used during bypass. In hypothermic patients, treatment with high-dose aprotinin resulted in significantly less reduced maximum platelet

aggregation and maximum gradient of platelet aggregation compared with the nontreated patients. Moreover, the recovery of platelet function was as quick as in the normothermic groups. This indicates that the undesirable abnormalities of platelet function during hypothermic CPB appear to be diminished when aprotinin is used. Blood loss and use of packed red cells and fresh frozen plasma were also significantly reduced when aprotinin was given in this situation.

One explanation for these results is that platelet membrane receptors, which are a prerequisite for guaranteeing intact platelet function, are particularly susceptible to alterations during hypothermic CPB. One of the assumed mechanisms by which aprotinin reduces bleeding is minimization of the loss of membrane receptor compounds (ie, GP 1b). Thus the major effect of aprotinin in this situation seems to be protection of the platelets at the molecular level [28].

The recovery of platelet function in the late postbypass period in *all* groups (including hypothermic patients without aprotinin) appears to be either due to restoration of platelet membrane receptors or due to arrival of young, hyperaggregating platelets from platelet pools in the lungs and bone marrow [23].

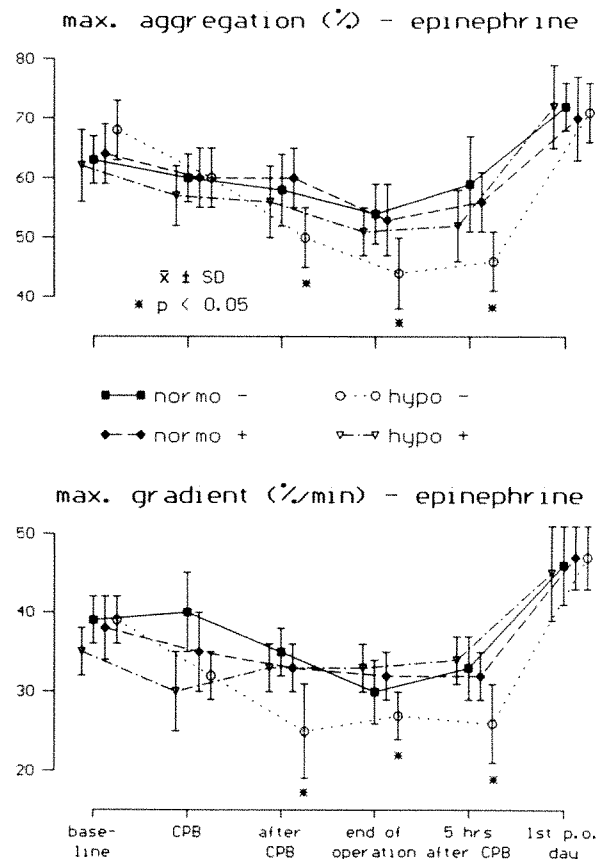


Fig 5. Changes in maximum (max.) platelet aggregation and maximum gradient of platelet aggregation induced by epinephrine (25 μ mol/L) compared with preoperative control. (SD = standard deviation; $\bar{x}$ = mean; other abbreviations are the same as in Figure 1.)

Interstudy comparisons of the use of aprotinin are difficult because of dissimilarities in the study conditions. The varying results are due partly to differences in type of oxygenator and pump, flow rates, suction techniques, degree of hypothermia, bypass times, and blood concentration techniques [12, 13, 23]. In some studies [9] that impressively demonstrated the beneficial effects of aprotinin, untreated control patients showed an *average* blood loss of approximately 1,200 mL with a standard deviation of approximately 600 mL after 24 hours. This indicated that some patients had a blood loss of approximately 3,000 mL postoperatively without having reoperation. The postoperative need for blood or blood derivatives was rather high (2.3 ± 2.2 units per patient) in these studies. In many of these studies, hypothermia was used, but the actual temperatures during bypass (blood, nasopharyngeal, and rectal) were not provided. Moreover, bubble oxygenators were often used although it has been reported that they predispose patients to hemostatic problems [33], and a cell saving device was used although it seems to be less effective in reducing blood loss than a hemofiltration device. In an extensive review of all recent studies dealing with aprotinin, Wildevuur [34] stated that the greater the blood activation and damage that occur, the greater the hemostatic benefits of aprotinin.

On the basis of these findings, we think that instead of the indiscriminate administration of aprotinin, it would be more logical to optimize perfusion conditions, by using a membrane oxygenator instead of a bubble oxygenator, normothermia instead of hypothermia, and hemofiltration rather than a cell saving device. Finally, the expertise of the surgeon markedly contributes to all attempts to limit blood loss in the postbypass period. When all these aspects are optimized, the role of aprotinin as a pharmacological device to improve platelet function and to reduce the use of homologous blood appears doubtful. As long as the risk/benefit ratio [35], the (weight-related?) dose, and even the mechanisms of its blood loss-reducing properties [27] are open to speculation, future controlled studies are warranted to answer these points concerning the efficacy of aprotinin in cardiac surgery.

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Notice From the American Board of Thoracic Surgery

The part I (written) examination will be held at the Hilton Executive Conference Center, Dallas Fort Worth Airport, Dallas, TX, on February 13, 1994. The closing date for registration is August 1, 1993.

To be admissible for the part II (oral) examination, a candidate must have successfully completed the part I (written) examination.

A candidate applying for admission to the certifying examination must fulfill all the requirements of the board in force at the time the application is received.

Please address all communications to the American Board of Thoracic Surgery, One Rotary Center, Suite 803, Evanston, IL 60201.

Topical Use of Aprotinin in Open Heart Operations

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Among various pharmacological agents used to reduce bleeding after open-heart operations, high-dose aprotinin therapy seems most promising. However, its long-term effects are still obscure; there is almost always possibility of bypass graft occlusions produced by the hypercoagulable state induced by aprotinin in coronary bypass operations. Topical application of aprotinin into the pericardial cavity could prevent the adverse effects. Fifty patients were prospectively studied to evaluate the effects of topical aprotinin. One million KIU of aprotinin was poured into the pericardial cavity before closure of

the sternotomy in group 1 (n = 25). Patients in group 2 (n = 25) served as controls. Total postoperative bleeding was significantly reduced in group 1 when compared with that of group 2 (722.7 ± 230.8 versus $1,282.6 \pm 225.7$ mL; $p < 0.01$). The use of banked donor blood products was significantly less in group 1 than in group 2 (0.33 ± 0.67 versus 1.36 ± 0.86 units; $p < 0.01$). These results show that topical use of aprotinin reduces postoperative blood loss and need for transfusion. It seems promising and warrants further studies to be done.

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Bleeding after cardiopulmonary bypass (CPB) is still a major problem facing cardiac surgeons. The harmful effects of CPB on the hemostatic mechanisms is well-known. The hemorrhagic diathesis associated with CPB has a wide range including thrombocytopenia, increased fibrinolysis, decreased clotting factors, unneutralized heparin, excessive protamine, and disseminated intravascular coagulation [1–4]. The actual incidence of life-threatening hemorrhage associated with CPB is in the range of 5% to 25% [4]. The fear of transmitting infectious diseases by transfusion of homologous blood and blood products, shortages of donor blood, and financial costs have led to development of a variety of blood-saving methods. These include normovolemic hemodilution, intraoperative autotransfusion, postoperative return of shed mediastinal blood, and the use of pharmacological agents such as prostacyclin, dipyridamole, desmopressin acetate, ϵ -aminocaproic acid, and aprotinin [5–7].

Aprotinin, a known inhibitor of plasmin and kallikrein [5, 6], has been shown to reduce bleeding in several studies [7–12]. Further studies are needed to clarify its mechanisms of action and to identify the long-term results. Adverse reactions to aprotinin, a history of acute pancreatitis, severe kidney and liver dysfunction, and most important the possibility of early graft closure in coronary artery bypass operations might prevent the routine use of aprotinin in open heart operations. Drawbacks of aprotinin have led us to use aprotinin topically in the pericardial cavity. This study was designed to show the effect of topical aprotinin in reducing postoperative blood loss.

Material and Methods

This study was conducted on 50 otherwise healthy male patients scheduled for elective coronary artery bypass grafting. Patients who received platelet-active drugs within 14 days of operation or who had any kind of bleeding diathesis were excluded from the study. Informed consent was obtained from all patients. They were randomly assigned to group 1 (aprotinin group) and group 2 (control group). Aprotinin (Trasylol; Bayer AG, Leverkusen, FRG) was supplied by the hospital pharmacy in bottles containing 50 mL of saline solution without any other additives or preservatives. Each milliliter of solution contained 10,000 kallikrein inactivator units (KIU) of aprotinin. Before closure of the median sternotomy, mediastinal and thoracic drains were clamped and 100 mL of aprotinin solution (1,000,000 KIU) at room temperature was poured into the pericardial cavity. The clamps on the mediastinal and thoracic drains were released after closure of the median sternotomy, and gravity drainage was allowed. After the patient was transferred to the intensive care unit, continuous low-grade suction supplemented with periodic milking of drains was applied.

The anesthetic management and conduct of CPB were standardized. All patients were premedicated with flunitrazepam (1 mg) orally and morphine (0.1 mg/kg) intramuscularly. Anesthesia was induced with flunitrazepam (0.02 mg/kg) and fentanyl (40 μ g/kg) given over 3 minutes. Pancuronium bromide (0.15 mg/kg) was used for muscle relaxation. The extracorporeal circuit consisted of a hollow-fiber membrane oxygenator (Terumo Copiox E, Terumo Co, Tokyo, Japan). Polyvinyl chloride tubing was used throughout the circuit except for the roller pump tubing, which was silicone rubber. Patients were heparinized before CPB with 300 U/kg heparin; whenever the

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Table 1. Patient Data^a

Variable	Group 1	Group 2	<i>p</i> Value
Age (y)	56.5 ± 6.8	58.7 ± 9.1	NS
CPB time (min)	90.7 ± 31.5	96.5 ± 31.7	NS
Total operative time (min)	159.8 ± 33.2	165.0 ± 32.9	NS
Average No. of distal anastomoses	3.22 ± 1.28	3.41 ± 0.96	NS
Preop hemoglobin (g/dL)	14.5 ± 0.8	14.3 ± 0.7	NS

^a Data are shown as mean ± standard deviation.

CPB = cardiopulmonary bypass; NS = not significant.

activated clotting time was shorter than 400 seconds, additional doses of heparin were given. After CPB, heparin was neutralized with protamine sulfate at a 1:1 ratio.

Mild to moderate hypothermia, cold crystalloid potassium cardioplegia (Plegisol; Abbott Laboratories, North Chicago, IL), and topical myocardial cooling with cold saline solution were employed for myocardial protection. Left internal mammary artery grafts supplemented with saphenous vein grafts were used routinely in all patients. The left pleural space was opened intentionally during left internal mammary artery harvesting.

The bleeding time, prothrombin time, activated partial thromboplastin time, and platelet counts were measured before the operation and when the patients arrived at the intensive care unit. The shed mediastinal blood was collected in a Receptaseal Thoracic autologous blood transfusion kit (Abbott Laboratories), and the amount was measured every half hour for the first day and hourly thereafter. The mediastinal and thoracic drains were removed when the total drainage was less than 100 mL over the previous 8 hours. Blood and blood components were administered only when the hematocrit value fell to less than 0.24 in the postoperative period. Shed mediastinal blood was not transfused in any patient during this study.

The number of grafts, duration of CPB, total operation time, cross-clamp time, incidence of reoperation for bleeding, amount of total chest tube drainage and total waste blood hemoglobin content were recorded for all patients. Plasma aprotinin levels were determined with the sandwich-enzyme-linked immunosorbent assay technique.

Student's *t* test was used for statistical analysis. A *p* value less than 0.05 was considered statistically significant. Data were reported as mean ± standard error of the mean. Statistical analyses were made using the Microstat (Ecosoft Inc, CA) statistical software package.

Results

There were no statistically significant differences between the two groups with regard to age, sex, duration of operation, CPB time, and average number of distal anastomoses (Table 1). There were also no significant differ-

ences between the two groups in postoperative hemodynamics, duration of intensive care, and postoperative hospital stay (data not shown).

Chest tube drainage in the first 24 hours was 420 ± 150 mL in the aprotinin group and 650 ± 225 mL in the control group (*p* < 0.05). Total postoperative chest tube drainage was 722.7 ± 230.8 mL (range, 300 to 1,100 mL) in group 1 (aprotinin) and 1,282.6 ± 225.7 mL (range, 750 to 1,700 mL) in group 2 (control) (*p* < 0.01) (Fig 1). The hemoglobin loss in the total chest tube drainage was 16 g in the aprotinin group and 49 g in the control group (*p* < 0.01). The color of drainage was pale. The drainage after the first 24 hours was mostly due to loss of tissue fluid. The use of banked donor blood products intraoperatively was not significantly different between two groups. However, the aprotinin group needed significantly less banked donor blood in the postoperative period (0.33 ± 0.67 versus 1.36 ± 0.86 units; *p* < 0.01). The percentages of patients receiving banked donor blood were 26.6% in the aprotinin group and 84.6% in the control group (*p* < 0.01).

Aprotinin levels were determined in 8 patients in the aprotinin group at the first hour after unclamping of the chest tubes. Aprotinin was not detected in any of the patients' blood.

Preoperative hemoglobin levels were not significantly different between the two groups. On postoperative day 1, the hemoglobin level was 9.1 ± 0.7 g/dL in the aprotinin group and 8.6 ± 0.9 g/dL in the control group (not significant).

There were no statistically significant differences between the two groups with regard to bleeding time, prothrombin time, activated partial thromboplastin time, activated clotting time, and platelet counts preoperatively and postoperatively.

None of the patients were reoperated on for bleeding.

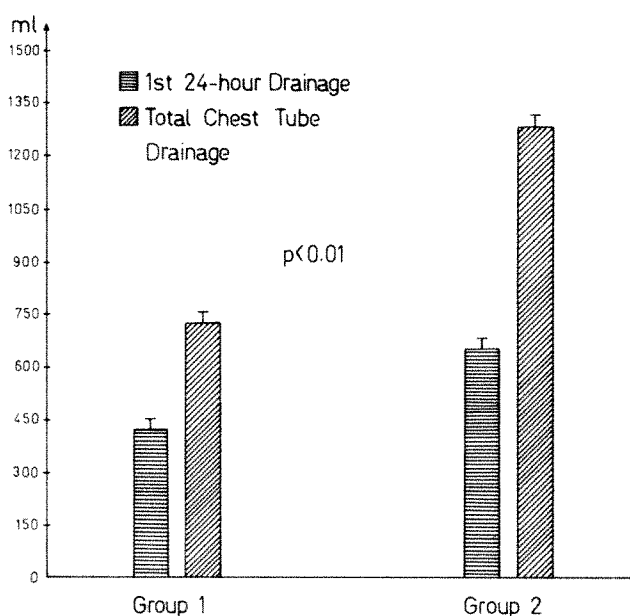


Fig 1. Postoperative blood loss.

All patients were discharged from the hospital in good condition.

Comment

Various clinical investigations have shown that high-dose aprotinin reduces postoperative blood loss significantly [7-12]. The mechanism of this effect remains unclear. Aprotinin exerts an inhibiting effect on proteolytic enzymes, forming an aprotinin-proteinase complex. It inhibits trypsin, plasmin, and tissue and plasma kallikreins [13]. Plasmin and kallikrein are generated by CPB; kallikrein activates Hageman's factor and activates plasminogen to form plasmin [14]. In low concentrations aprotinin inhibits plasmin completely, thereby inhibiting fibrinolysis, although at very high concentrations, inhibition of kallikrein reduces blood coagulability [15]. Royston and associates [8] and van Oeveren and co-workers [6] suggested that aprotinin exerts its effect by protecting the function of platelets. Further studies must be done to clarify aprotinin's mechanism of action.

Topical application of aprotinin into the pericardial cavity might prevent the adverse effects of aprotinin. The results of this study showed that topical use of aprotinin significantly reduced postoperative blood loss and the need for banked donor blood transfusions. The reduction in postoperative blood loss in our study was comparable with that in other studies in which the aprotinin was applied systematically [7, 11, 12]. This method of topical application of aprotinin will be especially useful in patients in whom the internal mammary arteries are used because the wound area, and thus bleeding, is more profound in these patients.

One hundred milliliters of aprotinin solution applied topically reduced the need for banked donor blood. In 18 of 25 patients no donor blood was used postoperatively. The reduction in use of banked donor blood could limit the problems associated with transfusion.

Dietrich and colleagues [11] reported that due to its effects on hemostasis, there is almost always the possibility of early graft closure with the use of aprotinin; further studies are needed to clarify this issue. Topical use of aprotinin will completely abolish this problem.

The total amount of aprotinin may be reduced by this method, which is important for the cost-benefit ratio.

Aprotinin could not be detected in any of the 8 patients' blood. This shows that the drug remains restricted to the pericardial space and the effect is completely due to topical action.

In conclusion, further studies must be done to explain the mechanism of topical aprotinin action. The use of aprotinin topically resulted in a significant reduction in postoperative blood loss and might be an alternative to its systemic use.

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Effects of Aprotinin on Anticoagulant Monitoring: Implications in Cardiovascular Surgery

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This study was designed to evaluate anticoagulant monitoring of heparin and platelet function in the presence of aprotinin. Aprotinin added to heparinized whole blood at concentrations equal to (30 $\mu\text{g/mL}$), twice, and four times that used in cardiopulmonary bypass operations synergistically elevated the activated clotting time (ACT) (536 ± 73 , 651 ± 86 , and 787 ± 71 seconds, respectively) over the value with heparin alone (384 ± 66 seconds) ($p < 0.001$). In addition, the ACT of heparin-protamine mixtures supplemented with protamine showed that the heparin was not completely neutralized (131 ± 12 versus 98 ± 7 seconds). Specific tests revealed that the effect on ACT caused by aprotinin is not equal to the anticoagulant effect of heparin. Thus there is a risk of underheparinization if the ACT is used as a monitor when aprotinin is present. Furthermore, protamine doses relative to

the heparin concentration, and not relative to the ACT, should be used to reverse heparin. In studying the effects of aprotinin on platelet function, there was a significant inhibition of aggregation when normal platelets were supplemented with aprotinin, but not for platelets of postoperative patients. This suggests that aprotinin may interact more favorably with nonactivated platelet surfaces, reducing or inhibiting the expression of receptors. Thus it is necessary to treat a patient with aprotinin before beginning cardiopulmonary bypass. Based on these data, the effect of aprotinin on the hemostatic system and its drug interactions must be considered to optimize safety and efficacy during cardiopulmonary bypass operations.

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Aprotinin has been used in many clinical situations to improve hemostasis in patients undergoing cardiopulmonary bypass (CPB) operations, with no reported side effects [1-6]. It inhibits kallikrein, plasmin, trypsin, chymotrypsin, and other proteases [7, 8], and it also affects receptors on platelet membranes [3, 5, 9, 10]. The decrease in blood loss in CPB operations with the use of aprotinin has been attributed to preservation of the adhesive capacity of platelets [2]; however, other mechanisms may also be affecting hemostasis.

We were interested in the effect of aprotinin on heparin dosage monitoring with the whole blood clotting time assay (ACT) during cardiac operations [11], particularly in view of recent clinical data showing increased thrombotic complications after cardiac operations with aprotinin [12]. Platelet-protamine interactions were also studied to further address the mechanism of action. Because aprotinin has not been released for clinical use in the United States, it was necessary to perform in vitro experiments. The combined heparin-protamine effect on the ACT in hemodiluted blood taken during cardiac operations from patients on CPB pump was also evaluated to anticipate possible perioperative procedural modifications.

Material and Methods

Study Design

This study was divided into three phases as follows.

PHASE 1. In vitro clotting times were performed using a stock concentration of 10.0 mg/mL aprotinin, which was added to pooled normal human plasma in a final plasma concentration range of 1.0 $\mu\text{g/mL}$ to 1.0 mg/mL ($n = 5$). Controls were plasma supplemented with saline solution. Prothrombin time (Dade, Miami, FL), activated partial thromboplastin time (APTT; Organon Teknika, Durham, NC), and Heptest, a clot-based heparin-sensitive APTT-like assay (Haemachem, St. Louis, MO) were performed. Aprotinin from Sanofi (Paris, France; lot VB101-RB22111) and Pentapharm (Basle, Switzerland; lot 5388/074) were compared.

PHASE 2. A second-phase (four parts) in vitro study used fresh whole blood collected from normal human subjects ($n = 10$). At each blood draw the first 3 mL was discarded and the remaining blood was aliquoted to syringes containing the solutions shown in Table 1.

Activated whole blood clotting time was measured immediately using the Hemochron 800 (International Technidyne, Edison, NJ) instrument. The remaining blood mixtures were placed in sodium citrate (9 mL blood to 1 mL citrate) and centrifuged for platelet-rich plasma and platelet-poor plasma. Platelet aggregation studies were then performed using a Bio/Data PAP-4 (Hatboro,

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Table 1. *In Vitro* Study Solutions

Part	Heparin	Aprotinin	Protamine Sulfate	Saline Solution	Owen's Veronal Buffer
A (4.5 mL blood)					
Syringe 1	...	0.5 mL Sanofi (0.3 mg/mL)	...	...	...
Syringe 2	...	0.5 mL Pentapharm (0.3 mg/mL)	...	...	...
Syringe 3	...	0.5 mL Sanofi (0.6 mg/mL)	...	...	...
Syringe 4	...	0.5 mL Pentapharm (0.6 mg/mL)	...	...	...
B (9.0 mL blood)					
Syringe 1	1.0 mL (25 U/mL)	None	...	...	...
Syringe 2	None	1.0 mL (0.6 mg/mL)	...	...	...
Syringe 3	0.5 mL (50 U/mL)	0.5 mL (1.25 mg/mL)	...	...	...
Syringe 4	0.5 mL (50 U/mL)	0.5 mL (2.25 mg/mL)	...	...	...
C (9.0 mL blood)					
Syringe 1	1.0 mL (25 U/mL)	None	None	...	...
Syringe 2	None	1.0 mL (0.3 mg/mL)	None	...	...
Syringe 3	0.5 mL (50 U/mL)	0.5 mL (0.6 mg/mL)	None	...	...
Syringe 4	0.5 mL (50 U/mL)	0.5 mL (0.6 mg/mL)	0.1 mL (2.25 mg/mL)	...	...
D (9.0 mL blood)					
Syringe 1	...	1.0 mL (0.3 mg/mL)	...	None	None
Syringe 2	...	1.0 mL (0.3 mg/mL)	...	0.5 mL	2.5 mL

PA) aggregometer. Final concentrations of arachidonic acid (33 $\mu\text{g/mL}$), adenosine diphosphate (2.5×10^{-6} mol/L), collagen (0.8 $\mu\text{g/mL}$), and epinephrine (10 $\mu\text{g/mL}$) were used to stimulate platelet aggregation. Hematocrits were measured in the hemodilution-simulated samples (part D).

PHASE 3. In a third phase of the study, blood obtained from patients undergoing CPB operations was evaluated ($n = 15$). Blood was drawn after anesthesia induction, 10 minutes after the initial heparin bolus (2.5 mg/kg), and 10 minutes after the entire protamine dose was given at the end of the operation. The initial 3 mL of blood was discarded, and the remaining 9 mL of blood was added to syringes containing either 1.0 mL of aprotinin (0.3 mg/mL) or 1.0 mL of saline solution. The ACT was measured immediately, and the remaining blood was used for aggregation studies as described above.

Laboratory results and patient information were obtained from the patients' medical records. All results are given as a mean $\pm$ one standard deviation.

Results

There were no significant changes in the prothrombin time, Heptest, or thrombin time at any concentration of aprotinin added in vitro to pooled human plasma. The APTT was elevated in a dose-dependent manner with aprotinin. The increase in APTT was 3 to 4 times baseline at a final plasma concentration of 1.0 mg/mL, and 1.5 to 2 times baseline at therapeutic concentrations (30 to 60 $\mu\text{g/mL}$ final plasma concentrations). The Sanofi and Pentapharm aprotinins showed comparable effects with no significant differences between the two drugs.

In the whole blood studies, there was a slight prolongation of the ACT to 126 ± 15 and 135 ± 19 seconds by

aprotinin added at a final blood concentration of 30 and 60 $\mu\text{g/mL}$, respectively ($p < 0.05$). The normal ACT for nontreated whole blood was 98 ± 7 seconds. There was a dose-dependent effect of aprotinin on the ACT. There were no significant differences between the Sanofi and Pentapharm aprotinins at the concentrations studied.

Heparin evaluated at a concentration identical to that used in CPB operations (2.5 U/mL blood) resulted in an ACT at the level desired during CPB operations, eg, 400 seconds. Addition of aprotinin (60 $\mu\text{g/mL}$) caused a synergistic anticoagulant response with heparin (ACT, 651 ± 87 seconds) elevating the ACT response above that caused by aprotinin (142 ± 9 seconds) or heparin (385 ± 66 seconds) alone or by a simple addition effect of the two agents (Fig 1). This effect was dose-dependent.

In a similar experimental setting, the effect of protamine was studied. The anticoagulant effect of heparin was completely reversed with protamine used at the ratio of 1 mg protamine to 100 U heparin, but protamine did not neutralize the aprotinin effect (Fig 2). With protamine added, the ACT of the aprotinin-heparin group (see Fig 2, bar 4) returned to the level of the nonheparinized but aprotinin-added group (see Fig 2, bar 1). A baseline level of 98 ± 7 seconds was not achieved; the aprotinin anticoagulant effect remained.

In an attempt to establish conditions similar to those in a patient undergoing CPB, 33% hemodiluted (buffer plus saline solution) blood was evaluated with aprotinin supplementation. The decrease in hematocrit was similar to that seen in CPB patients during operation (0.40 ± 0.04 decreased to 0.24 ± 0.05). The ACT was slightly but not significantly elevated in the hemodiluted blood in comparison with the normal blood (149.1 ± 13.9 versus 133.9 ± 10.9 seconds) with aprotinin supplementation (30 $\mu\text{g/mL}$).

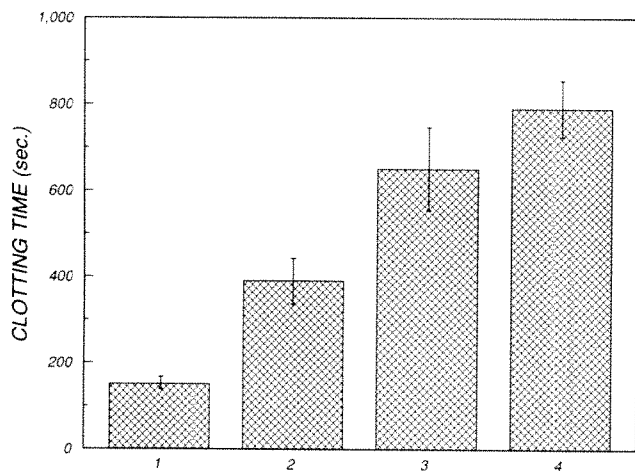


Fig 1. Effect of aprotinin and heparin on the activated clotting time in normal volunteers. Group 1 = aprotinin (60 µg/mL); group 2 = heparin (2.5 U/mL); group 3 = aprotinin (60 µg/mL) + heparin (2.5 U/mL); and group 4 = aprotinin (125 µg/mL) + heparin (2.5 U/mL). Results are given as a mean $\pm$ 1 standard deviation (n = 10). Aprotinin added to heparin produces a synergistic response on the activated clotting time.

The effect of aprotinin in blood obtained from patients while on CPB during operation was similar to that reported above for the hemodiluted bloods of normal donors. There was once again a synergistic anticoagulant effect of aprotinin with heparin, and there was a return to the aprotinin ACT value after addition of protamine (Fig 3).

For the supplemented blood collected from normal volunteers, the maximum platelet aggregation response and the slope of aggregation for all agonists tested in the aprotinin-supplemented platelet-rich plasma was signifi-

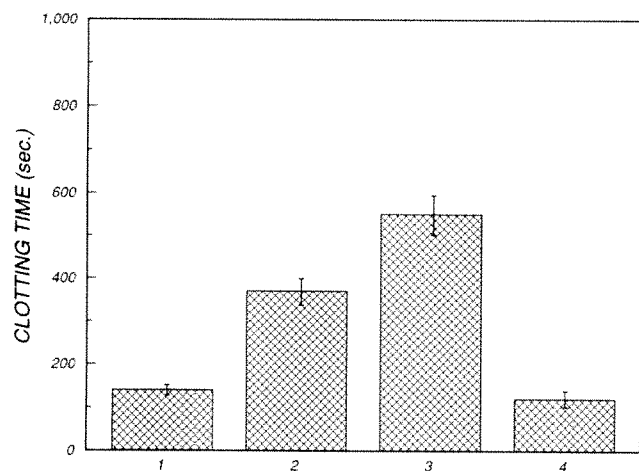


Fig 2. Effect of aprotinin, heparin, and protamine on the activated clotting time in normal volunteers. Group 1 = aprotinin (30 µg/mL); group 2 = heparin (2.5 U/mL); group 3 = aprotinin (30 µg/mL) + heparin (2.5 U/mL); and group 4 = aprotinin (30 µg/mL) + heparin (2.5 U/mL) + protamine (25 µg/mL). Results are given as a mean $\pm$ 1 standard deviation (n = 10). Protamine sulfate reverses the anticoagulant effect of heparin but not of aprotinin.

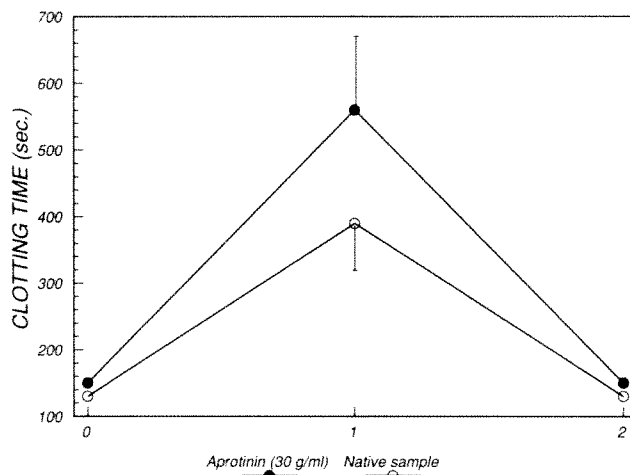


Fig 3. Effect of aprotinin supplementation on the activated clotting time during cardiopulmonary bypass operation. Time 0 = anesthesia; time 1 = 10 minutes after pump; and time 2 = after protamine infusion. Results are given as a mean $\pm$ 1 standard deviation (n = 15). Aprotinin synergistically elevated the activated clotting time response in the presence of heparin; protamine sulfate did not reverse the anticoagulant response of aprotinin in patients.

cantly decreased from non-aprotinin-supplemented samples ($p = 0.001$), although individual variations were observed (Fig 4). There were no significant differences between the various aprotinin concentrations tested. The decrease in slope of aggregation was related to an inhibition of the onset of the second wave of aggregation. The most remarkable finding was the disaggregation response seen in the aprotinin-supplemented samples when adenosine diphosphate was used as an agonist (Fig 5). This was not observed with the other agonists (collagen, epinephrine, arachidonic acid).

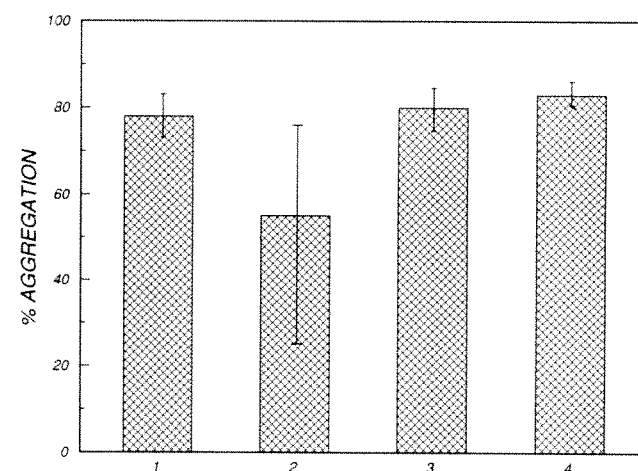


Fig 4. Platelet aggregation in the presence of aprotinin. Platelets of normal volunteers were activated with adenosine diphosphate. Group 1 = heparin (2.5 U/mL); group 2 = aprotinin (60 µg/mL); group 3 = heparin (2.5 U/mL) + aprotinin (60 µg/mL); and group 4 = heparin (2.5 U/mL) + aprotinin (125 µg/mL). Results are given as a mean $\pm$ 1 standard deviation (n = 10). Platelet aggregation induced by collagen, epinephrine, and arachidonic acid showed similar results.

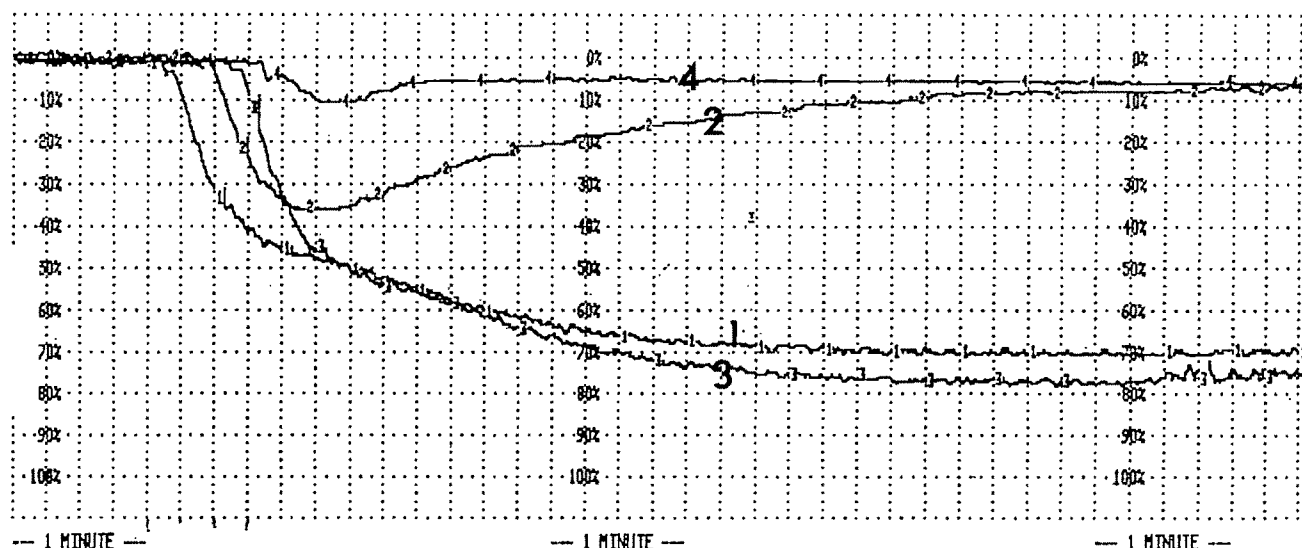


Fig 5. Typical platelet aggregation response of normal volunteer platelets supplemented with aprotinin, heparin, protamine sulfate, or a combination. Adenosine diphosphate was used as an aggregating agent. Line 1 = heparin (2.5 U/mL); line 2 = aprotinin (30 µg/mL); line 3 = heparin (2.5 U/mL) + aprotinin (30 µg/mL); line 4 = heparin (2.5 U/mL) + aprotinin (30 µg/mL) + protamine (25 µg/mL). Note no effect by heparin alone on platelet aggregation (group 1) but platelet disaggregation (reversibility) in groups 2 and 4.

The presence of heparin eliminated the inhibitory effect of aprotinin. In the presence of heparin plus protamine, the inhibition of platelet aggregation by aprotinin could be observed (Fig 5).

In CPB patients the platelet aggregation decreased, as expected, as the operation progressed; we attributed this to both dilutional and traumatic effects to the platelets by the CPB pump. Contrary to what was found in normal human donors, there was no significant difference in aggregation response in the ex vivo aprotinin-supplemented and nonaprotinin groups for any intraoperative or postoperative sample. Moreover, there was a trend toward an increase in the aggregation response when aprotinin was added ex vivo to patient blood taken after protamine was given.

Comment

This study was mainly designed to examine aprotinin's effects on anticoagulant monitoring, namely the ACT, which is used at many institutions to monitor the anticoagulant level in CPB patients intraoperatively. An attempt was also made to evaluate the effects of aprotinin on platelet function due to the reported clinical effects observed [5, 10].

Our in vitro studies showed that the APTT was elevated in a dose-dependent fashion most likely via the inhibitory effects of aprotinin on kallikrein and thus the contact/intrinsic system. There were no effects on the other aspects of the coagulation profile (prothrombin time, thrombin time, Hep-test), demonstrating that the anticoagulant effect of aprotinin observed by the ACT is not heparinlike. Although there was an increase in the ACT

with aprotinin supplementation, because this anticoagulant effect cannot be attributed to a heparinlike quality, it is not appropriate to assume that the aprotinin synergistic enhancement of the ACT would allow for reduced heparinization [12].

For adequate anticoagulation with heparin, the goal during CPB operation is to maintain an ACT of 400 seconds [13]. This dose effect has worked well in the past. However, with new drug treatments the relationship between the heparin dose and the ACT response can be modified. For a given ACT response (eg, 400 seconds) in CPB patients who are given aprotinin, lower doses of heparin would actually be used than in patients not given aprotinin because aprotinin also affects the ACT. Because the aprotinin effect is not heparinlike, and it has not been shown that patients can be adequately anticoagulated during CPB with lower heparin doses, adverse side effects could be observed. This may be one explanation for the increased incidence of myocardial infarction observed in a recent clinical trial of aprotinin [12]. Controlled trials must be performed to examine this, looking in particular for renal, cerebral, and cardiac insufficiency.

Protamine reversal of heparin, in the presence of aprotinin, neutralized the synergistic anticoagulant effect of heparin but not the anticoagulant effect of aprotinin. Therefore, in CPB patients given aprotinin, protamine doses relative to the heparin concentration in the body, and not relative to the ACT, should be used to reverse the effect of heparin at the end of a cardiac operation. Furthermore, when used with hemodiluted blood, there was an increase in the ACT over nonhemodiluted aprotinin-supplemented blood, but this effect was most probably

due to the hemodilution and not a stronger aprotinin effect.

The second phase of this study using normal volunteers showed that there was an inhibition of platelet aggregation induced by epinephrine, adenosine diphosphate, arachidonic acid, and collagen in vitro in both the aprotinin- and aprotinin/heparin/protamine-supplemented groups. However, with only aprotinin and heparin, platelet aggregation was unaltered. In the ex vivo CPB patient study, contrary results were obtained. The inhibitory effect of aprotinin supplementation was not observed in blood obtained from CPB patients immediately after coming off pump. Aprotinin appears to interact more favorably with the glycoprotein receptors of nonactivated platelets than of activated platelets, delaying aggregation. This could theoretically preserve platelet integrity by decreasing the activation response of the platelets caused by the traumatic effect of the CPB pump and heparin exposure. Thus aprotinin would only be effective when patients are pretreated before exposure of the platelets to the CPB pump or other mechanisms of platelet activation.

Preservation of platelet function is thought to be important to reduce postoperative blood loss. However, further studies, including thromboxane and prostaglandin measurements, need to be performed on patients receiving aprotinin intraoperatively to identify the extent of platelet activation in individual patients. It has been shown that hyperactive platelets contribute to thrombotic risk [14]. Whether aprotinin treatment produces a relative hyperactivity of platelet function in all or some of the CPB surgical patients should be determined and related to thrombotic clinical events associated with aprotinin use.

Furthermore, aprotinin inhibits the fibrinolytic system. At this early stage of using aprotinin clinically, it is important to evaluate the individual patient's preoperative fibrinolytic status. It is known that patients have variable levels of the fibrinolytic parameters [15], and that patients with cardiovascular disease have abnormal activity levels [16]. As there are individual responses to heparinization, it is likely that there will be individual responses to aprotinin. Thus, whether the best clinical approach will be an unadjusted dose or a patient-tailored dose with a contraindication for use in specific patients remains to be determined.

The fact that aprotinin affects the ACT response, which is used to determine heparin dosing, the fibrinolytic system, and platelet aggregation suggests the need for conducting more comprehensive experimental and clinical studies on aprotinin to determine optimal dosing regimens.

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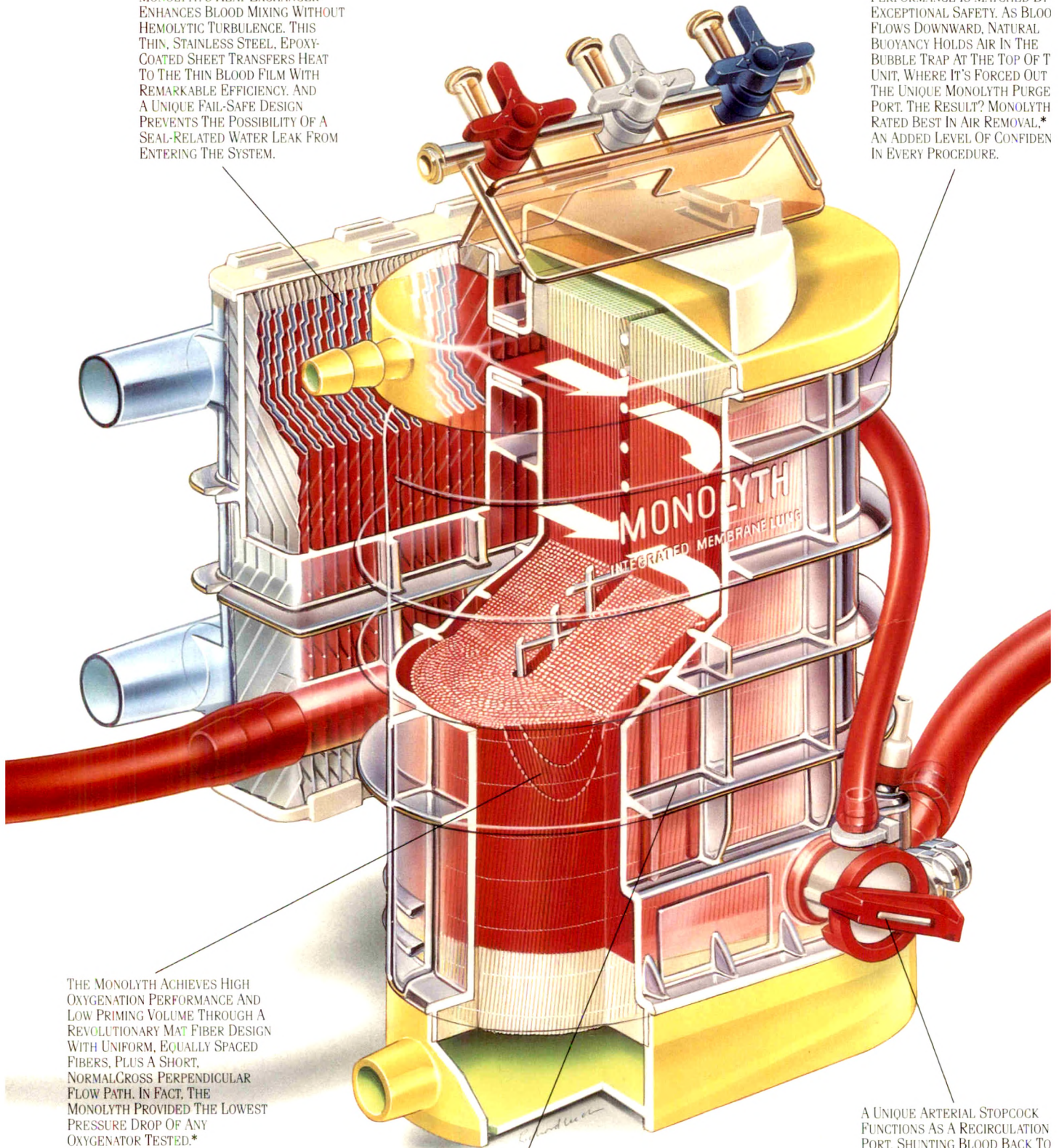
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Effects of External Stenting on Wall Thickening in Arteriovenous Bypass Grafts

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Late occlusion of the saphenous vein graft appears to result in part from wall thickening as an adaptation to increased mean wall stress. Using an established pig model of arteriovenous bypass grafting, the effect of reducing wall stress with an external porous polytetrafluoroethylene stent was investigated. Segments of autologous saphenous vein were implanted by end-to-end anastomoses into both carotid arteries, with one graft supported by a stent 4 mm in diameter. Increases in graft wall dimensions were quantified 4 weeks later by computer-aided planimetry of transverse histological sections. The contribution of hyperplasia (i.e., cell proliferation) to the changes observed was further clarified by measurements of DNA concentration. All grafts showed an increase in external size, but this was restricted by stenting. All grafts also showed an increase in cross-

sectional area of the tunica media and tunica intima that was only partly accounted for by an increase in DNA concentration, which indicated that both hyperplasia and hypertrophy had occurred. Stented grafts showed less enlargement of the media but greater enlargement of the intima. Overall wall size was therefore similar in stented and unstented grafts. Stented grafts showed less increase in DNA concentration than unstented grafts. In stented grafts, the residual luminal cross-sectional area was significantly less than in unstented grafts. The data show that external stenting reduces medial enlargement and hyperplasia but increases encroachment of the intima into the lumen. Because final luminal size is thought to be of paramount importance in maintaining long-term patency, external stenting is unlikely to be of benefit.

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Autologous saphenous vein continues to be one of the most widely used conduits for revascularization of coronary and peripheral arteries despite its disappointing long-term patency rate [1-3]. Late occlusion appears to be the result of both the intimal thickening caused by migration and proliferation of smooth muscle cells and the appearance of mature lipid-laden atherosclerotic plaques [3-5]. Both these processes probably represent adaptive changes by the vein to its insertion into the arterial system [3-5]. Factors potentially responsible for these changes may include the increased mean wall tension and the increased mean shear stress. If so, the use of an external support to limit the effect of wall tension might reduce the degree of wall thickening. To test this hypothesis, we used a previously described pig model of arteriovenous bypass grafting [6] to quantify the effects of a rigid external polytetrafluoroethylene support on the changes in intimal and medial size of the vein graft and in cell numbers reflected by DNA concentration.

Material and Methods

Surgical Procedures

Studies were performed using 15 white race pigs initially weighing 20 to 25 kg. Premedication, induction and maintenance of anesthesia, and autologous saphenous

vein to carotid artery bypass grafting were performed as detailed previously [6]. Briefly, a longitudinal incision was made on the outer aspect of the hind leg to expose approximately 12 cm of the long saphenous vein. The vein was dissected free from surrounding tissue using a "no-touch" technique [7], and all side branches were secured with a 6-0 Prolene ligature. Then the vein was removed, gently irrigated with a heparinized isosmotic sodium chloride solution (0.9 g/L), and stored in the same solution at room temperature for 20 to 40 minutes until needed.

The common carotid artery was isolated through a longitudinal neck incision, and a 3- to 4-cm segment, isolated between vascular clamps, was excised. Both cut ends were beveled to approximately 45 degrees. A segment of reversed saphenous vein was similarly beveled and then anastomosed end-to-end to the carotid artery using a continuous 7-0 Prolene suture (Ethicon, Somerville, NJ). On the opposite side, after the proximal anastomosis was completed, the vein was passed through a polytetrafluoroethylene tube (Gore-Tex, W. L. Gore & Associates Inc, Elkton, MD) 4 mm in diameter and slightly longer than the graft, after which the distal anastomosis was performed. A single 6-0 Prolene suture was used to secure the polytetrafluoroethylene graft to the adventitial tissue of the two divided ends of the carotid artery. The neck and leg wounds were closed in layers, and the animals were allowed to recover.

After 4 weeks, the animals were anesthetized as before, the neck was opened, and the graft was identified. The carotid artery was transected distal to the graft, and the

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absence of blood flow was taken to indicate graft occlusion. Only patent grafts were used for analysis because graft occlusion was associated with extensive fibrotic changes that obscured the vein structure.

Microscopic Methods

The graft was removed and divided in two, and the larger segment was cannulated at one end with a syringe attached to a mercury manometer [8]. The other end of the graft also was cannulated and the cannula, was clamped. Fixative, consisting of a solution of 10% formalin in 0.1 mol/L sodium phosphate buffer, pH 7.3, was pumped into the lumen of the vessel for 5 to 10 minutes to achieve a pressure of approximately 100 mm Hg. The smaller segment was frozen in liquid nitrogen for estimation of DNA concentration. A segment of long saphenous vein from the other hind leg, ie, ungrafted vein, was obtained at the time of graft removal and was treated similarly.

Fixed grafts and ungrafted segments of vein were further fixed, dehydrated, cleared, and embedded in paraffin wax with their axis perpendicular to the cutting plane. Sections were cut at four levels approximately 0.75 mm apart, mounted on glass slides, stained with Miller's elastic stain, and counterstained with van Gieson's stain. Luminal, intimal, and medial cross-sectional areas were measured for three sections at each level by computer-aided planimetry using a Nikon microscope with a camera lucida, Hewlett-Packard computer (HP 85; Corvallis, OR), a digitizing tablet, and Graphic Information System quantitation program V3.0.

The area enclosed by the endothelium defined the lumen. The area between the endothelium and the internal elastic lamina defined the intima. The area between the internal and external elastic laminae defined the media. Luminal encroachment was defined as the percentage of the area enclosed by the internal elastic lamina occupied by the intima.

Mean values were then calculated for all sections from the same graft. Average intimal thickness was calculated from the cross-sectional area data using the following formulas and assuming that the sections consisted of circular profiles, which was a valid assumption because the tissues were fixed at normal perfusion pressure:

- (1) Luminal radius = $\sqrt{\text{luminal area}/\pi}$
- (2) Intimal thickness
 $= \sqrt{(\text{intimal} + \text{luminal area})/\pi} - \text{luminal radius}$
- (3) Medial thickness
 $= \sqrt{(\text{medial} + \text{intimal} + \text{luminal area})/\pi}$
 $- \text{luminal radius} - \text{intimal thickness}$

DNA Concentration

Frozen vessels were thawed, the adventitia was removed, and the remaining tissue was weighed and then homogenized at 4°C using a motor-driven Teflon glass homogenizer with 100 volumes of 0.3 mol/L perchloric acid until a

smooth suspension was created. The DNA concentrations were then measured as detailed previously and were expressed as micrograms per milligram of wet weight [6]. The total DNA concentration ($\mu\text{g}/\text{mm}$ graft length) was calculated as the product of DNA ($\mu\text{g}/\text{mg}$ wet weight) multiplied by wall area (mm^2), the assumption being that the tissue density was $1 \text{ mg}/\text{mm}^3$.

Echocardiographic Doppler Sonography

A Sonicaid Vasoflo III continuous-wave Duplex ultrasound system (Oxford Sonicaid, Chichester, West Sussex, England) was used to produce simultaneously a high-resolution image and the flow pattern within the grafts 10 to 20 minutes after completion of the surgical procedure, as previously described [6]. The diameters of the carotid artery, the in situ saphenous vein, and the grafts were measured at five points along their length, and the mean diameter was calculated.

Statistical Analysis

Values are shown as the mean $\pm$ the standard error of the mean with the number of observations in parentheses. Unless otherwise stated, significance between groups was established with Student's *t* test using unpaired values.

Results

All operations were performed by the same surgeon (G.D.A.). One pig failed to survive until the grafts were recovered and hence was excluded from the analyses. Unstented grafts had a patency rate of 93% ($n = 14$) and stented grafts, 79% ($n = 14$) ($p =$ not significant).

Diameter Measurements and Flow Pattern

Ultrasound measurements were made to determine the effect of stenting on the initial diameter of the vein grafts. The mean luminal diameter of the proximal and distal carotid artery at the level of grafting was $3.1 \pm 0.2 \text{ mm}$ and $3.0 \pm 0.1 \text{ mm}$, respectively ($n = 5$). Ungrafted in situ saphenous vein had a mean luminal diameter of $2.2 \pm 0.3 \text{ mm}$ ($n = 5$). Unstented grafts had a mean diameter of $3.6 \pm 0.2 \text{ mm}$ ($n = 4$) and stented grafts, $3.7 \pm 0.3 \text{ mm}$ ($n = 4$).

Ultrasound measurements were also used to determine whether stenting affected flow patterns in the grafts. Velocity at peak systole and diastolic flow were comparable in the proximal carotid artery and in both unstented and stented grafts, implying similar flow rates (Fig 1). Flow inhomogeneity (related to turbulence) quantified by Doppler spectral broadening at peak systole was similar in the middle point of both unstented and stented grafts ($54.1\% \pm 0.5\%$ and $53.8\% \pm 0.2\%$, respectively; $n = 4$).

Changes in Luminal, Medial, and Intimal Size and DNA Concentration

In ungrafted vein, the intima consisted of a confluent monolayer of endothelium. The media, which was composed of an average of ten smooth muscle cell layers, was surrounded by well-defined internal and external elastic laminae (Fig 2A).

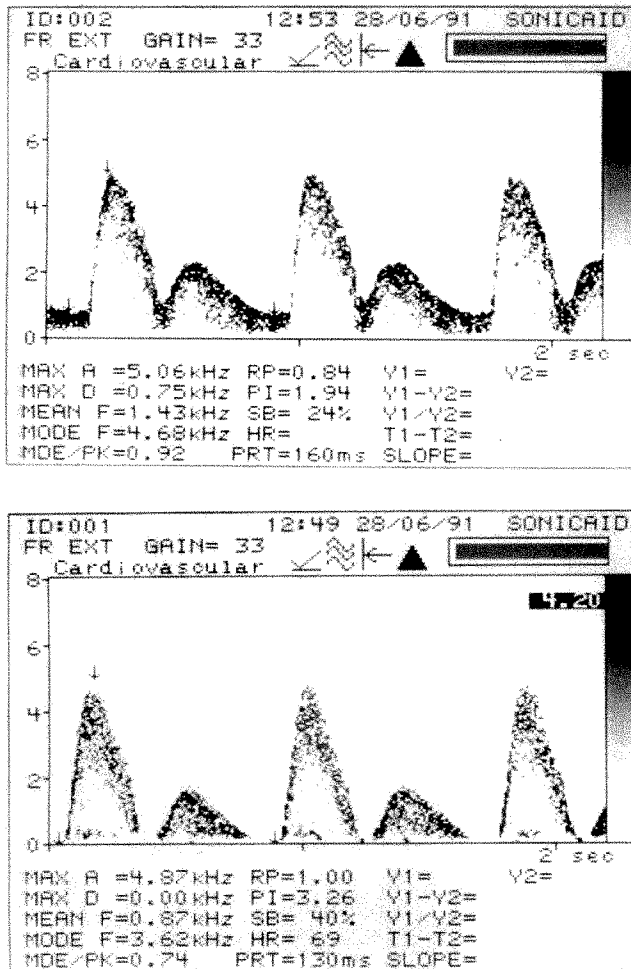


Fig 1. Sonograms illustrating spectral flow pattern from (A) un-stented and (B) stented grafts.

In unstented and stented grafts recovered after 4 weeks, the internal elastic lamina remained unchanged, whereas the external elastic lamina became more separated (Figs 2B, 2C). A new intimal layer with both axially

Table 1. Changes in Medial, Intimal, and Luminal Areas^a

Variable	Vein (n = 24)	Unstented Graft (n = 13)	Stented graft (n = 11)
Medial area (mm ²)	1.1 ± 0.2	5.09 ± 0.63 ^b	2.25 ± 0.33 ^{b,c}
Intimal area (mm ²)	0	2.49 ± 0.45 ^b	3.98 ± 0.64 ^b
Total wall area (mm ²)	1.1 ± 0.2	7.59 ± 0.85 ^b	6.23 ± 0.20 ^b
Luminal area (mm ²)	2.3 ± 0.3	11.18 ± 1.33 ^b	1.87 ± 0.3 ^c
Luminal encroachment (%)	0	14.4 ± 2.7 ^b	55.3 ± 5.2 ^{b,c}

^a Data are shown as the mean ± the standard error of the mean; the number of observations is in parentheses. ^b Significance: $p < 0.01$ versus vein. ^c Significance: $p < 0.001$ versus unstented graft.

and circumferentially oriented smooth muscle cells was clearly present in both unstented and stented grafts (see Figs 2B, 2C).

Medial and intimal cross-sectional areas were increased by grafting. Medial cross-sectional areas increased significantly more in unstented grafts (4.6-fold) compared with stented grafts (twofold) (Table 1). In contrast, the final intimal cross-sectional area was only about half as great in unstented as in stented grafts, although the difference did not reach significance ($p = 0.1$). As a result of these inverse changes, there was no significant difference in total wall area (intimal + medial cross-sectional areas) between unstented and stented grafts. Luminal areas increased approximately fivefold in unstented grafts compared with veins but remained virtually unchanged in stented grafts (see Table 1). As a result, luminal encroachment was significantly less in unstented than stented grafts (see Table 1).

The DNA concentration per milligram of wet weight was lower in all grafts than in ungrafted vein (Table 2), as demonstrated previously [9]. This indicated that the density of viable cells had declined. The DNA concentration per milligram of wet weight was significantly greater in unstented than stented grafts (see Table 2), which indicated that the final density of viable cells was greater in unstented grafts. The calculated DNA concentration per

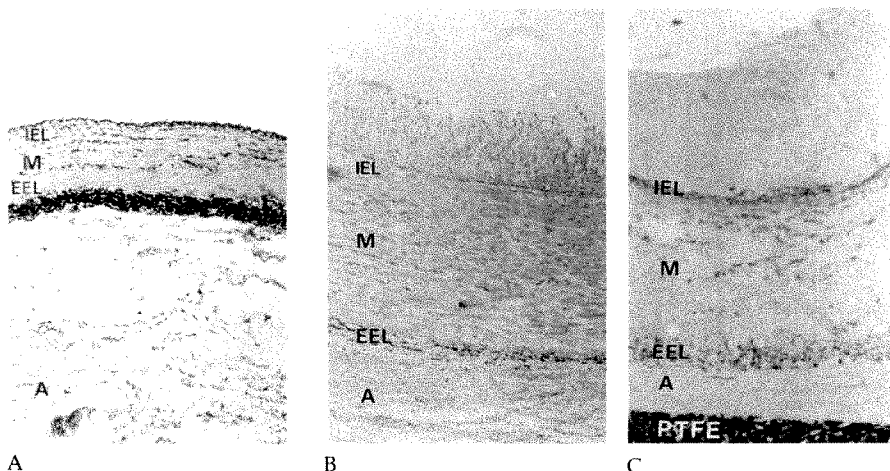


Fig 2. Transverse sections of (A) un-grafted vein, (B) unstented graft, and (C) stented graft. (Miller's elastin stain and van Gieson's stain as counterstain; $\times 75$ before 24% reduction.) (A = adventitial tissue; EEL = external elastic lamina; IEL = internal elastic lamina; M = media; PTFE = polytetrafluoroethylene.)

millimeter of length was significantly increased by grafting (see Table 2), which demonstrated that grafting caused an overall increase in vessel wall cell numbers. The DNA concentration per millimeter of length was significantly greater in unstented than stented grafts (see Table 2) as a result of the increased cell density.

The results of the planimetry measurements were also used to calculate mean external radii and medial and intimal thicknesses. Consistent with the increase in graft size, unstented grafts showed a 2.4-fold increase in external radius (Table 3). This was much reduced in stented grafts (1.6-fold). Wall thickness (intimal + medial thicknesses) was increased 4.1-fold in unstented grafts and significantly more, 6.1-fold, in stented grafts (see Table 3). The difference between unstented and stented grafts was due to greater intimal thickening partly compensated by less medial thickening in the stented grafts (see Table 3). As a net result, luminal radius was significantly less in stented than unstented grafts (see Table 3).

Comment

Late saphenous vein graft failure remains a major problem in coronary and peripheral artery revascularization with up to 50% of vein grafts occluded by 10 years postoperatively [2, 3, 10]. Previous studies have demonstrated that short-term graft patency may be improved by antiplatelet agents [3] or by optimal techniques of harvesting [6]. Late graft attrition, however, is influenced only marginally by antiplatelet agents or surgical technique [3, 9, 10] and thus probably represents an intrinsic adaptation of the vein to its insertion in the arterial circulation. The higher pressure and flow velocities in the arterial circulation result in increases in both mean wall tension and mean shear stress. Either or both of these factors may cause smooth muscle cell migration into the intima and subsequent proliferation [4, 11].

Surrounding the graft by a rigid external support has the theoretical advantage that wall tension will eventually be reduced or even eliminated. By limiting graft expansion, however, mean shear stress will be greater than in unstented grafts. The axial pressure pulse will be unaltered. The net effects of these differences are difficult to predict, and therefore the effect of stenting on the changes in wall dimensions was investigated empirically.

Table 2. Changes in DNA Concentrations^a

Variable	Vein (n = 24)	Unstented Graft (n = 13)	Stented Graft (n = 11)
Measured DNA concentration ($\mu\text{g}/\text{mg}$ wet wt)	2.7 ± 0.2	0.986 ± 0.15^b	$0.546 \pm 0.09^{b,c}$
Calculated DNA concentration ($\mu\text{g}/\text{mm}$ length)	1.97 ± 0.3	7.45 ± 1.41^b	$3.87 \pm 0.70^{b,c}$

^a Data are shown as the mean $\pm$ the standard error of the mean; the number of observations is in parentheses. ^b Significance: $p < 0.05$ versus vein. ^c Significance: $p < 0.05$ versus unstented graft.

Table 3. Changes in Wall Dimensions^a

Variable	Vein (n = 24)	Unstented Graft (n = 13)	Stented Graft (n = 11)
External radius (mm)	1.02 ± 0.15	2.4 ± 0.09^b	1.60 ± 0.07^c
Wall thickness (mm)	0.14 ± 0.01	0.57 ± 0.07^b	$0.85 \pm 0.09^{b,c}$
Medial thickness (mm)	0.14 ± 0.01	0.37 ± 0.05^b	0.24 ± 0.03^c
Intimal thickness (mm)	0	0.21 ± 0.04^b	$0.61 \pm 0.10^{b,c}$
Luminal radius (mm)	0.98 ± 0.13	1.85 ± 0.12^b	0.74 ± 0.07^c

^a Data are shown as the mean $\pm$ the standard error of the mean; the number of observations is in parentheses. ^b Significance: $p < 0.01$ versus vein. ^c Significance: $p < 0.05$ versus unstented graft.

The results demonstrated that grafting led to an increase in vessel wall thickness accompanied by an increase in DNA concentration per millimeter of length. Thus hyperplasia of smooth muscle cells contributed to the increase in wall size. Nevertheless, the DNA concentration per milligram of wet weight fell, which implies that hypertrophy of cells and laying down of extracellular matrix also took place. Stenting with relatively rigid polytetrafluoroethylene had little net effect on wall thickening because lesser medial thickening was accompanied by greater intimal thickening. Stenting resulted in a reduction in DNA concentration per millimeter of graft length, which implies that less hyperplasia occurred and is consistent with the concept that wall tension is a determinant of hyperplasia. Stenting was also accompanied by a reduction in DNA concentration per milligram of wet weight, which implies that stented grafts had a relatively greater degree of hypertrophy or deposition of extracellular matrix. Owing to the restricted expansion of the stented grafts, the external radius of grafts was reduced by stenting. This together with a greater degree of intimal thickening resulted in greater encroachment into the vessel lumen and a reduction in residual luminal size. Stenting therefore increased predicted mean shear stress at the endothelial surface, although based on previous studies, this is associated with less rather than more intimal proliferation in both arteries [12] and arteriovenous bypass grafts [11]. Alternative explanations for the greater intimal thickening we observed are that preventing graft expansion forced smooth muscle cells into the intima physically, or that interruption of regrowth of adventitial vessels may have caused greater hypertrophy, consistent with previous work [13].

Two other studies [14, 15] have examined the effect of external stenting on vein graft adaptation to the arterial circulation. Barras and colleagues [14] demonstrated that stenting decreased intimal thickness in a sheep model. The number of animals studied was small, however, and different animals were used for test and controls. In addition, the much thinner jugular vein was used, and the grafts were not pressure fixed. Perhaps for these

reasons, Barras and colleagues were unable to locate the internal elastic lamina and therefore measured intimal thickness as the distance from the subendothelial basal lamina to the beginning of the elastic external layer, which is equivalent to total wall thickness in our study.

Kohler and colleagues [15] examined the effect of rigid external support on a rabbit model of arteriovenous bypass grafts. They also were unable to distinguish between the media and intima, but concluded that stenting did not reduce overall wall thickness. In agreement with our study, greater luminal encroachment occurred in the stented grafts, and this led to a smaller final luminal size. The study of Kohler and colleagues [15], however, was compromised by the fact that the proximal part of the graft was wrapped with polytetrafluoroethylene and the distal part of each graft was left to act as the corresponding control. The wrapping of the proximal part of the graft may have altered the local flow dynamics and may have influenced the degree of wall thickening in the control section. We confirmed that contralateral stented and unstented grafts had similar flow patterns, and so the differences between stented and unstented grafts are unlikely to result from differences in initial flow patterns.

In conclusion, this study demonstrates that although external support leads to a reduction in smooth muscle hyperplasia, intimal thickening is promoted. This suggests that other factors such as constraining expansion of the vessel, greater shear stress, or interruption of the adventitia by the stent are also important determinants of wall thickening. The balance of factors is such that stenting of grafts leads to reduced luminal size. If directly applicable to the clinical situation, our results suggest that stenting is unlikely to increase long-term graft patency.

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Completion Pneumonectomy and Thoracoplasty for Bronchopleural Fistula and Fungal Empyema

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Achieving sterilization of the postpneumonectomy space and bronchial healing may be difficult when active granulomatous infection of the pleural space and lung parenchyma is present at the time of operation. Three patients with chronic bronchopleural fistula, fungal empyema, and fungal cavities of the remaining ipsilateral lobe were managed with one-stage completion pneumonectomy and modified eight-rib thoracoplasty. Two patients had infection with *Aspergillus fumigatis* and 1 patient had *Coccidioides immitis*. Two patients had received mediastinal radiation after prior upper lobectomy for carcinoma of the lung. Two patients were having massive hemoptysis at the time of pneumonectomy.

Eight-rib thoracoplasty with suturing of the intercostal muscles to the bronchial stump was performed on all patients. In 2 patients a mass closure of hilar vessels and bronchus was used because of inability to individually close the vessels and bronchus due to ligneous scarring of the hilum. Antibiotic and antifungal irrigations into the operative area were used postoperatively. Chest tubes were left in place 6 to 8 weeks. All wounds healed primarily. Patients were alive without recurrent local infection or tumor at follow-up 3 to 13 years postoperatively.

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Achieving bronchial stump closure and control of pleural space infection is often difficult when pneumonectomy is performed in the presence of both pleural space and lung parenchymal granulomatous infection [1]. Experience with completion pneumonectomy for benign conditions has shown that the mortality and morbidity is high. The Mayo Clinic found 27.6% mortality and major complications in 55.2% of patients when completion pneumonectomy was performed for benign disease. The principal causes of death were related to uncontrolled hilar hemorrhage at the time of operation and multiorgan system failure after persistent pleural space infection postoperatively. The Mayo Clinic group postulated that muscle transposition to reinforce the bronchial stump and obliterate the pleural space might contribute to reducing the mortality [2].

We have performed completion pneumonectomy and simultaneous eight-rib thoracoplasty in 3 patients with postlobectomy bronchopleural fistula, fungal empyema, and active fungal infection of the remaining lobe. The purpose of this report is to describe the surgical techniques and management of these patients. The surgical techniques included methods for controlling the hilar vessels, reinforcing the bronchial stump, and obliterating the pleural space.

Patients and Methods

The characteristics of the 3 patients are shown in Table 1. All patients had persistent fungal infection in the empyema cavity and in cavities in the remaining lobe that was

refractory to antifungal therapy. Two patients had the additional complication of massive hemoptysis from empyema, lung cavities, or both. Two patients had received hilar and mediastinal radiation. In every patient no alternative to pneumonectomy was considered a satisfactory option in managing the infection or hemoptysis.

The extensive fungal infection of the empyema cavity and the remaining lung made sterilization of the postpneumonectomy space virtually impossible. Tissue coverage of the bronchial stump was considered desirable to achieve healing of the bronchial closure. Thoracoplasty was performed to obliterate the pleural space and to cover the bronchus with viable muscle.

In 2 patients the effects of radiation and fungal infection had produced such ligneous scarring and induration of the hilum of the lung that individual ligation and closure of pulmonary vessels and bronchus was found to be impossible. The techniques used for closing the vessels and bronchus, performing the modified eight-rib thoracoplasty, and covering the bronchus with intercostal muscle are shown in Figures 1 through 7. The entire hilum is transfixed with multiple mattress sutures of 3-0 Prolene (Ethicon, Somerville, NJ). As the pulmonary artery and vein are divided they are oversewn with running 3-0 Prolene. The bronchus is oversewn with interrupted 3-0 Prolene. Additional sutures are placed in the tissue surrounding the bronchial stump. Decortication of the parietal pleura is performed.

Ribs one through eight are removed subperiosteally from the costovertebral junction to just lateral to the articulation with the cartilaginous ribs. The extent of rib resection and the number of ribs resected are determined at the time of operation. Sufficient ribs are removed to allow collapse of the chest wall against the mediastinum

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Table 1. Patient Characteristics

Variable	Patient No.		
	1	2	3
Age (y)	32	56	58
Sex	Female	Female	Female
Previous interventions			
Prior lobectomy	Right upper	Right upper	Left lower
Original pathology	Carcinoma	Carcinoma	Coccidioidomycosis
Radiation	100 Gy ^a	50 Gy	None
Condition when pneumonectomy/ thoracoplasty performed			
Time since lobectomy (y)	2	3	10
Massive hemoptysis	Yes	No	Yes
Bronchial fistula	Yes	Yes	Yes
Empyema organism	<i>Aspergillus fumigatis</i>	<i>Aspergillus fumigatis</i>	<i>Coccidioides immitis</i>
Previous drainage of empyema	No	Yes	No
Foreign body in empyema cavity	Yes ^b	No	No
Cavities in remaining lobe	Yes	Yes	Yes
Cavities in opposite lung	No	No	No
Follow-up			
Duration (y)	13	3	3
Status	Alive, no tumor	Alive, no tumor	Alive

^a Sixty grays external radiation, 40 Gy interstitial radiation after lobectomy.

^b The foreign body was a sheet of silicone rubber material that had been placed at the original lobectomy in preparation for irradiation with iridium 192 after loading needles.

and elevated diaphragm to completely obliterate the pleural space and have viable muscle in contact with the mediastinum, diaphragm, and hilar structures.

The peribronchial sutures above the bronchus, and the peribronchial sutures below the bronchus are passed through

three adjacent intercostal bundles. These sutures are tied to attach the intercostal muscles to the bronchial stump.

Chest tubes are placed into the space deep and superficial to the intercostal muscles. An irrigation catheter is placed beneath the intercostal muscle layer in the upper portion of the thorax. In my patients the chest tubes were left in place 6 to 8 weeks. Antibiotics and antifungal agents (amphotericin) were continuously infused into the irrigation catheter. The antibiotic and antifungal agents were determined by cultures and sensitivities of the chest



Fig 1. The hilum of the right lung has been isolated. The empyema has been evacuated and the pleural and mediastinal adhesions divided. No plane of dissection around hilar vessels and bronchus could be identified. The divided azygos vein is shown.

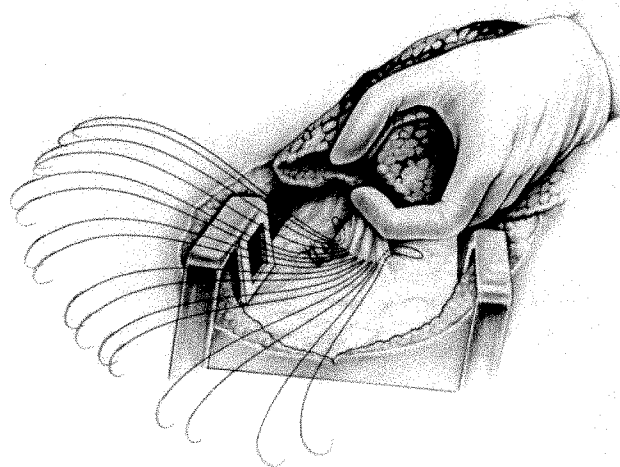
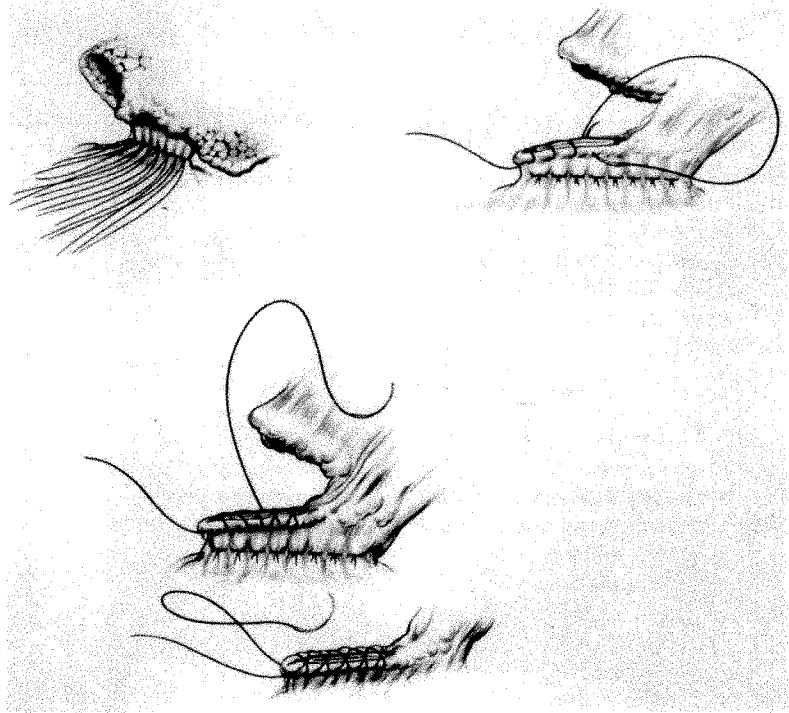


Fig 2. Mattress sutures of 3-0 Prolene were placed through the hilum of the lung to include pulmonary vessels and bronchus.

Fig 3. In the upper left portion of the figure the mattress sutures have been tied. The upper right portion shows that as the pulmonary artery and vein are divided, the vessels are oversewn with 3-0 Prolene. In the lower center of the figure the oversewing is completed.



tube drainage. All patients received amphotericin solution through the irrigation catheter. The chest tubes were slowly removed after the drainage diminished, the consistency cleared, and absence of cavity formation was demonstrated by chest roentgenography and sinograms through the chest tubes. All wounds healed primarily, and no secondary drainage of abscesses or fluid collections was required.

Results

Patients were followed up 3 to 13 years. There was no recurrence of tumor in the 2 patients whose original resection was for carcinoma of the lung. There was no recurrence of infectious complications in the hemithorax. There has been no evidence of infection related to the gutter created by retention of the transverse processes of the vertebrae. One patient required bronchoscopic re-

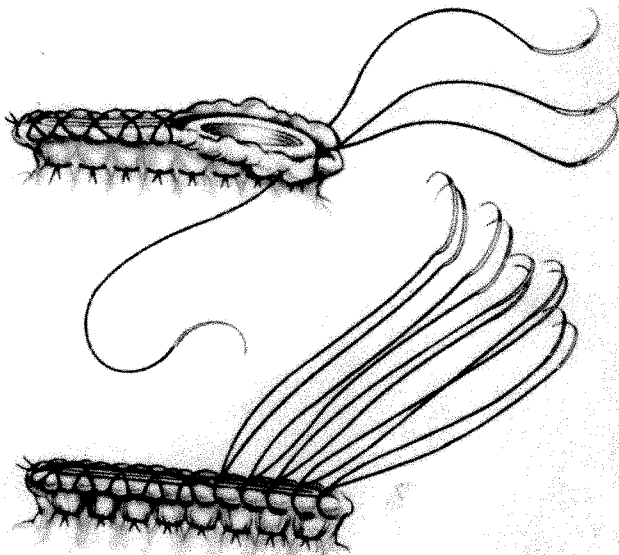


Fig 4. The upper portion of the figure shows that the bronchus has been divided. In the lower portion the stump of the bronchus has been closed with interrupted 3-0 Prolene. These sutures are left long so that they may be used to secure the intercostal muscles to the bronchus after the modified eight-rib thoracoplasty.

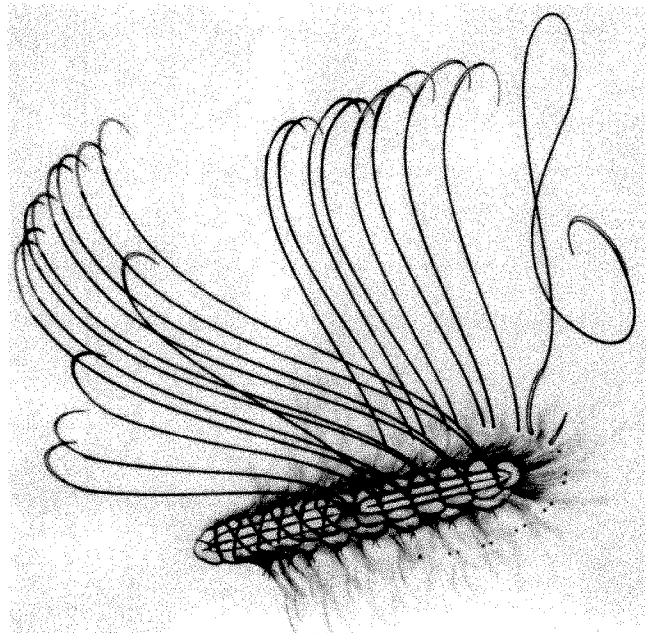


Fig 5. Sutures of 3-0 Prolene are placed in the tissue surrounding the bronchial stump. These sutures will be passed through the intercostal muscles to secure the muscle to the bronchus.

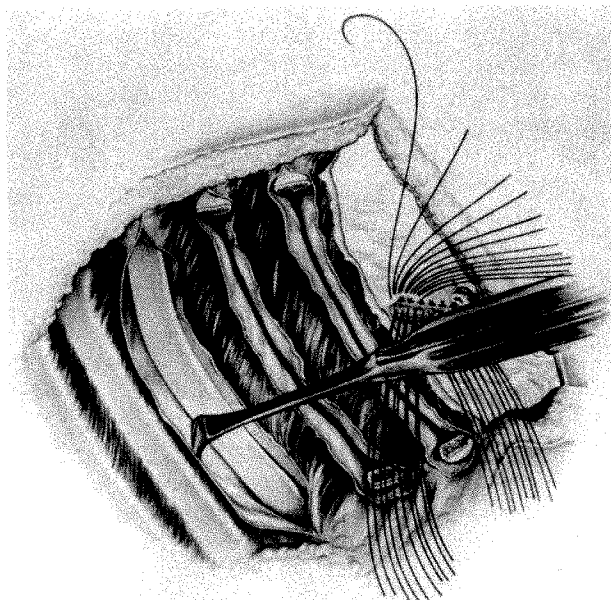


Fig 6. Ribs one through eight are resected subperiosteally from the costovertebral articulation posteriorly to just lateral to the junction with the cartilaginous ribs.

removal of a Prolene mattress suture from the bronchial stump 3 years postoperatively. Figures 8 and 9 show the posteroanterior chest roentgenogram of patient 1 before the operation and 6 months after the operation.

Comment

In the Mayo Clinic experience with completion pneumonectomy, operative death caused by uncontrollable hem-

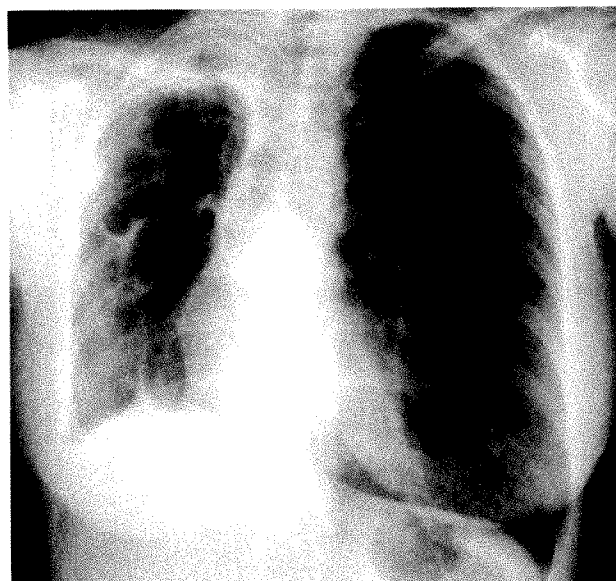


Fig 8. This is the preoperative posteroanterior chest roentgenogram of patient 1. There is air in the fungal empyema at the apex of the right pleural space. The remaining lower lobe contains numerous cavities.

orrhage typically occurred in patients with benign disease who had previous mediastinal radiation and obliteration of the pericardial space [2]. Others have recommended intrapericardial control of the difficult pulmonary artery at the time of completion pneumonectomy [3, 4]. My colleagues and I chose not to explore the pericardial space because of concern that we might spread the fungal infection to the pericardial cavity. Obliteration of the pericardial space is common in patients having comple-

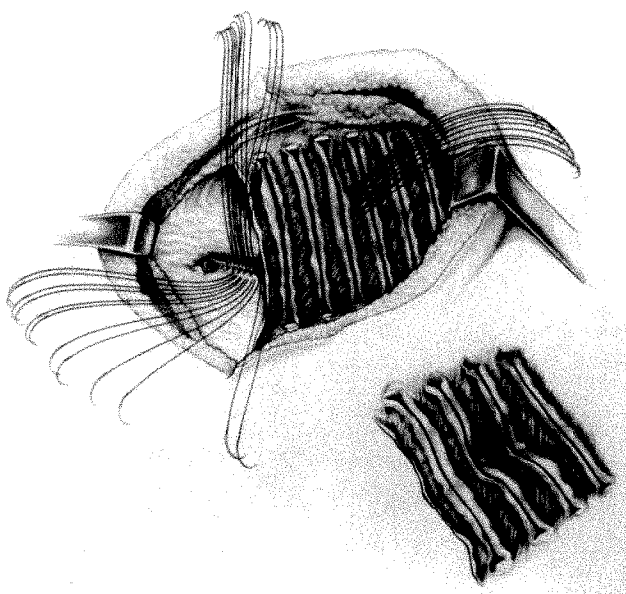


Fig 7. The left side of the figure shows the bronchial and peribronchial sutures being passed through the intercostal muscles. The sutures are passed through three adjacent intercostal muscle bundles. The right side of the figure shows the position of the intercostal muscles after the bronchial and peribronchial sutures have been tied.

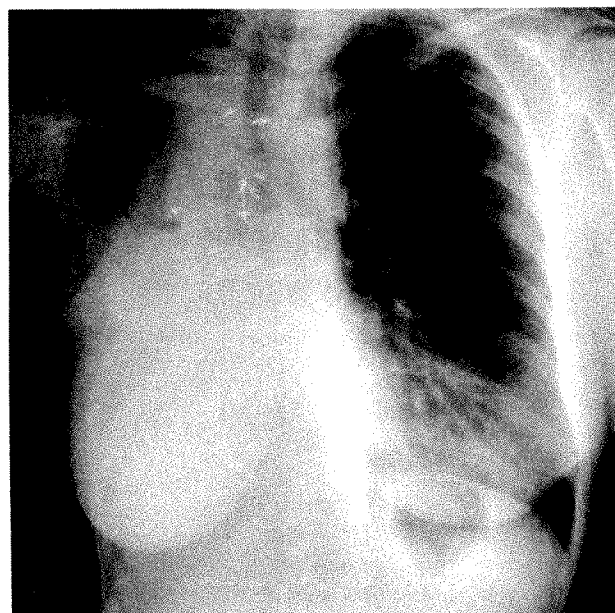


Fig 9. The chest roentgenogram of patient 1 6 months after operation shows complete obliteration of the right pleural space. The left lung has remained free of active infection.

tion pneumonectomy [2]. The technique of closure of the hilum of the lung with horizontal mattress sutures that we describe has the advantage of being applicable in virtually every situation without opening the pericardium.

Thoracoplasty for the management of postpneumonectomy empyema has been recommended by several authors in recent years [5, 6]. Some authors have recommended leaving the first rib but resecting the costovertebral articulation and portions of the transverse processes of the thoracic vertebrae [6]. We chose to resect the first eight ribs including the first rib but to leave the costovertebral articulation undisturbed. Tube drainage of the pleural space after thoracoplasty is recommended for several weeks [6]. The pleural space was completely obliterated in all our patients with the costovertebral junction left intact. It is our impression the complete obliteration of the space is facilitated by prolonged tube drainage along with continuous antibiotic and antifungal irrigation.

We were impressed by the progressive clearing of the drainage from the collapsed pleural space as antibiotic and antifungal solutions were continuously irrigated into the area. Other authors have recommended the local irrigation of antifungal solutions after pulmonary resection for aspergillosis [7]. The radiation effects and scarring of the mediastinal pleura may delay the healing and obliteration of the space and diminish the local concentrations of systemic antibiotics and antifungal agents.

Physical deformity and incapacity due to chest wall changes have not been severe in our patients. One of our patients returned to full-time employment and has been capable of fairly strenuous activities including skiing. The degree of function in these patients has been comparable with the functional state we have observed in patients after intrathoracic transposition of extrathoracic muscle for closure of bronchial fistulas. The blood loss associated with these operations was not excessive. Use of the electrocautery has greatly diminished the blood loss associated with thoracoplasty in my experience. Recent experi-

ence with intrathoracic muscle transposition after pneumonectomy shows that patients require multiple procedures (1 to 19; median, 5). Failure to achieve chest wall healing and bronchial closure was common (16% and 14.3% respectively) after intrathoracic muscle transposition [8]. In my opinion, the thoracoplasty closure technique herein described is a more certain method of obliterating infected thoracic spaces and achieving chest wall healing and bronchial closure than is transposition of muscle. Prolonged tube drainage with instillation of antimicrobials into the infected space is important in achieving these results.

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Cardiopulmonary Bypass Procedures in Dialysis Patients

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To determine the operative outcome of chronic renal failure patients, we retrospectively reviewed twenty-five consecutive adult patients with chronic renal failure dependent on maintenance hemodialysis (21) or peritoneal dialysis (3), who underwent cardiopulmonary bypass procedures over a five-year period in our institution. The operations included isolated coronary artery bypass grafting in 16 patients; aortic valve replacement in 3; aortic valve replacement plus mitral valve replacement in 1; aortic valve replacement, mitral valve replacement, and coronary artery bypass grafting in 2; aortic valve replacement and coronary artery bypass grafting in 1, mitral valve replacement and coronary artery bypass grafting in 1, and repair of a thoracoabdominal aortic aneurysm in 1 patient. Fourteen operations were elective, and 11 were urgent or emergent. The number of patients with good (>0.50), fair (0.30 to 0.50), and poor (<0.30) left ventricular ejection fractions were 13, 9, and 3, respectively. There were 0, 7, 7, and 11 patients in New York Heart Association functional classification I, II, III, and IV, respectively. All patients were dialyzed within 24 hours before operation. All but 3 patients were managed by immediate postoperative peritoneal dialysis via a Technoff catheter placed intraoperatively (18 patients) or via a preexisting Technoff catheter (4 patients). This

was then switched to hemodialysis when clinical conditions stabilized. Univariate analysis of 22 preoperative and intraoperative variables, followed by a multivariate analysis with a stepwise logistic regression model, was performed using the 30-day or in-hospital operative mortality as the dependent variable. The urgency of the operation and New York Heart Association class IV were found to be independent variables associated with increased operative mortality. There were no operative deaths among the 14 patients having elective operation; 4 of the 11 patients having nonelective operation died postoperatively, constituting a 36% operative mortality for this subgroup. All operative deaths occurred in the patients in preoperative New York Heart Association class IV (4/11 or 36%). This study demonstrated that elective cardiopulmonary bypass operations can be performed in chronic renal failure patients with excellent operative outcome, when done with careful perioperative management. Patients having nonelective operations and patients in the most advanced stage of their cardiac diseases had substantial operative mortalities in this series. The overall operative mortality of the 296 cases reported in the English-language literature thus far is 9%.

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The feasibility of general surgical procedures has been demonstrated in patients with chronic renal failure [1, 2]. In the procedures that require the use of cardiopulmonary bypass (CPB), the problems in the management of their perioperative care are accentuated and unique problems arise. Special attention is needed to address the ongoing problems in the balance of fluid and electrolytes, the maintenance of adequate red cell mass, perioperative bleeding diathesis, and the timing and route of perioperative dialysis. Since the first report of valvular operations done on 2 patients with renal failure in 1968 [3], 30 subsequent reports on a variety of cardiopulmonary surgical procedures done on these patients have been published in the English-language literature [2-32]. A total of 278 cases has been reported in the literature thus far, and we report an additional 25 adult dialysis-dependent pa-

tients who underwent operative procedures that required the use of CPB over a 6-year period in our institution. The morbidity and mortality of our series are presented in conjunction with a literature review. The emphasis of this article is on the perioperative management of the dialysis patient who undergoes a CPB procedure.

Patients and Methods

In the period 1985 to 1991, 25 patients had a preoperative diagnosis of chronic renal failure during their hospital stays for any CPB procedures according to the computer data files of the medical record department of The New York Hospital-Cornell University Medical Center. These charts were reviewed in detail regarding the preoperative data, as well as the operative and postoperative course. Coronary artery stenosis was considered clinically significant when more than 75% of the lumen was occluded. Left ventricular ejection fraction was obtained from the cardiac catheterization or radionuclear cineangiography reports. The operations were considered elective when the patients were admitted to the cardiothoracic surgery ser-

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vice electively to have their operations on the following day. They were considered nonelective if the patients were receiving intravenous nitroglycerin or heparin for unstable angina, or requiring inotropic agents or mechanical ventilatory support for cardiopulmonary instability in the preoperative period.

Perioperative factors that were analyzed for their association with operative mortality included sex; age; the type of operation (coronary artery bypass grafting [CABG], valvular replacements, or CABG with valvular replacements); urgency of operation; left ventricular ejection fraction; preoperative New York Heart Association (NYHA) functional classification; previous myocardial infarction; arrhythmia; hypertension; diabetes mellitus; cerebrovascular disease; peripheral vascular disease; chronic pulmonary disease; smoking history; gastrointestinal diseases; preoperative ongoing infection; hematologic disease; lengths of anesthetic, cardiopulmonary bypass, and aortic cross-clamp times; postoperative transfusion requirement; the volume of postoperative mediastinal bleeding; and the need for mediastinal reexploration.

Patients with major hypertension and chronic obstructive pulmonary disease included any receiving long-term medications. Patients with cerebrovascular disease included all with a history of strokes or transient ischemic attacks, and those with peripheral vascular disease included only patients with a history of claudication or peripheral vascular operations (or both). All patients underwent standard cardiopulmonary bypass with a Cobe membrane oxygenator (Cobe Laboratories, Inc, Denver, CO) at moderate hypothermia (25° to 28°C), with pump flow rates of 1.8 to 2.2 L · min⁻¹ · m⁻² to maintain venous oxygen saturation greater than 60% and perfusion pressures greater than 50 mm Hg. The extracorporeal circuit was routinely primed with isotonic crystalloid solution (Normosol; Abbott Laboratories, North Chicago, IL), and fresh blood was added to maintain a minimum hematocrit of 0.24. Myocardial protection was achieved by cold sanguineous hyperkalemic solution and topical cooling with iced slush or cold saline solution. An autotransfusion device (Cell Saver; Haemonetics Braintree, MA) was used to concentrate suctioned mediastinal blood during operation. Patients were rewarmed to a bladder temperature of at least 35°C before the discontinuation of CPB. Operative mortality included deaths occurring within 30 days of the operation or during the same hospitalization.

Fisher's exact test was used for the nonparametric variables, and unpaired *t* test was used for continuous variables in the univariate analysis. All the variables that were associated with operative mortality with a *p* value less than 0.10 were entered into a multivariate logistic regression analysis with stepwise elimination, and coefficients were computed by the method of maximum likelihood. A *p* value less than 0.05 was considered to be statistically significant. Continuous variables are presented as means ± standard deviation when appropriate. Analysis was performed using the BMDP statistical software package (BMDP Statistical Software, Inc, Los Angeles, CA) on a PC-type computer. Literature review was

Table 1. Patient Profile

Variable	Number
Total No. of Patients	25
Sex (M/F)	15/10
Age (y)	
Mean	62
Range	45-78
Preoperative dialysis	
Duration (mo)	33 ± 65
Type	
Hemodialysis	22
CAPD	3
NYHA classification	
I	0
II	6
III	7
IV	11
LVEF	
Good (>0.50)	13
Fair (0.30-0.50)	9
Poor (<0.50)	3
Urgency of operation	
Elective	13
Urgent	12
Emergent	0
Type of operation	
CABG	16
VR	4
VR + CABG	4
TAAA	1
No. of grafts/patient	2.6 ± 0.9
Aortic cross-clamp time (min)	57 ± 33
CPB time (min)	105 ± 51
Associated diseases	
Diabetes	9
Hypertension	22
Cerebrovascular disease	3
Peripheral vascular disease	6
Arrhythmia	4

CABG = coronary artery bypass grafting; CAPD = continuous ambulatory peritoneal dialysis; CPB = cardiopulmonary bypass; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; TAAA = thoracoabdominal aortic aneurysm repair; VR = valvular replacement.

searched through the Medline files dated back to 1960 in the National Library of Medicine using the modem-operated software Grateful.Med (Bethesda, MD). This was supplemented by the references of the identified articles.

Results

These 25 patients had at least 1 month of dialysis with a mean duration of 33 months before their operative procedures (Table 1). Three patients were maintained on chronic ambulatory peritoneal dialysis, and the others on hemodialysis. The preoperative NYHA classification and

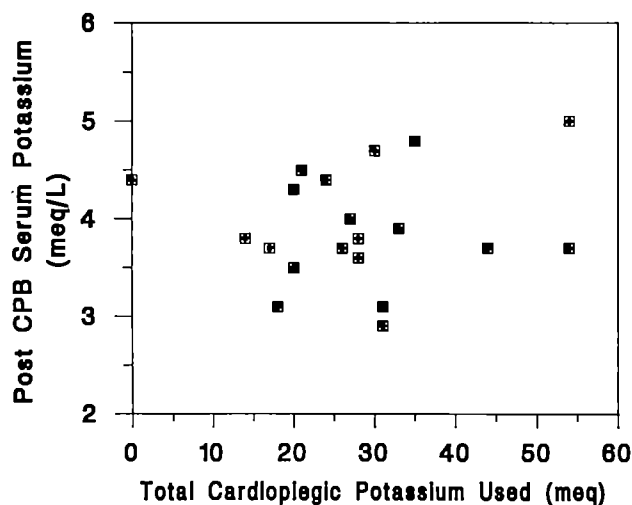


Fig 1. Correlation of postoperative serum potassium level with amount of infused cardioplegic potassium. (CPB = cardiopulmonary bypass.)

left ventricular ejection fraction are listed in Table 1. The NYHA classification of the patient with the thoracoabdominal aortic aneurysm repair is not included. About half of the operations were elective, and the procedures were predominantly CABG. The number of coronary conduits placed ranged from 1 to 5, with a mean of 2.6. The aortic cross-clamp time ranged from 17 to 155 minutes with a mean of 57 minutes, depending on the complexity of the procedure. Cardiopulmonary bypass was used without cardioplegic arrest in the patient with the thoracoabdominal aortic aneurysm repair. A variety of associated diseases are listed in Table 1, with hypertension being the most common. Anemia was, as expected, found in all of these patients due to their renal failure. Polycystic kidney disease ($n = 5$) and diabetes ($n = 4$) are the two most common causes of renal failure in this group of patients. Other causes included hypertension (2 patients), membranous glomerulonephritis (2), renal artery disease (1), poststreptococcal glomerulonephritis (1), and unknown (4). Five patients had chronic renal failure caused by acute tubular necrosis secondary to prerenal causes and contrast toxicity (3 and 2 patients, respectively).

The total amount of potassium given in the cardioplegic solution during operation did not correlate with the serum potassium measured upon arrival to the intensive care unit from the operating room (correlation coefficient = 0.14) (Fig 1). The zero data point represents the patient with the thoracoabdominal aortic aneurysm repair without cardioplegic arrest. This information could not be accurately obtained from the records of 5 patients. There was always a net decrease in the immediate postoperative serum potassium level as compared with the preoperative values (4.56 ± 0.15 mEq/L preoperatively versus 3.91 ± 0.12 mEq/L postoperatively; $p = 0.0016$ by paired t -test). The immediate postoperative serum potassium level also did not correlate with the total anesthesia length (range, 3.4 to 13.3 hours), CPB time (range, 35 to 266 minutes), or aortic cross-clamp time (range, 17 to 155 minutes), with correlation coefficients of 0.22, 0.20, 0.28, respectively.

A total of 10 major and 8 minor complications occurred in these 25 patients (Table 2). Two of the 3 patients with a history of cerebrovascular disease suffered postoperative strokes that were ultimately the cause of their demise. There were three major gastrointestinal complications, two of which required surgical resection for a dead intraabdominal viscus. One of these 2 patients died. One patient with upper gastrointestinal hemorrhage was successfully treated with conservative management. Surprisingly, there were only two minor primary infectious complications (see Table 2) and there were no cases of sternal wound infection.

Postoperative mediastinal bleeding in excess of 1 L in the first 12 hours developed in 1 patient, who was taken back to the operating room for reexploration. The amount of postoperative blood loss and transfusion requirements of these 25 renal patients were compared with that of a cohort of 30 consecutive patients who underwent elective isolated CABG in 1989 (Table 3). The renal patients had similar amounts of blood loss in the first 12 and the second 12 hours after leaving the operating room. Although not statistically significant, the number of units of red cells used was higher in the renal group than the control group. More importantly, the proportion of patients requiring the perioperative use of red cell transfusion was significantly higher in the renal group than in the control group. This was due to the more frequent intraoperative use of red cells, because the preoperative hematocrit was significantly lower in the renal group than in the control group (0.31 ± 0.04 versus 0.41 ± 0.05 , respectively; $p < 0.05$ by unpaired t test). Likewise, the frequencies of platelet and fresh frozen plasma uses were significantly higher in the renal group than in the control group (see Table 3).

The median lengths of intensive care unit, telemetry unit, and postoperative hospitalization stays for these patients were 3 days (range, 1 to 70 days), 8 days (range, 0 to 37 days), and 16 days (range, 11 to 100 days), respectively.

There were a total of four operative deaths. One oc-

Table 2. Postoperative Complications

Complication	Number
Major	
Bleeding/tamponade	1
Myocardial infarction	1
Cerebrovascular accident	2
Respiratory failure	2
Gastrointestinal ^a	3
Peripheral vascular ^b	1
Minor	
Transient arrhythmia	4
Heart block ^c	1
Seizure	1
Leg wound cellulitis	1
Peritoneal dialysis catheter infection	1

^a Cholecystitis, ischemic colitis, hemorrhage. ^b Embolism. ^c Required a permanent pacemaker.

Table 3. Postoperative Blood Loss and Transfusion Requirements^a

Variable	Control ^b	Renal Patients	<i>p</i> Value
Chest tube output (mL)			
0-12 hours	511 ± 221	554 ± 317	NS
12-24 hours	260 ± 112	251 ± 155	NS
Transfusions, first 3 days (units)			
Red cells	2.2 ± 1.8 (23)	5.3 ± 5.4 (21)	0.0179 ^c
Platelets	1.4 ± 3.4 (5)	1.6 ± 1.9 (14)	0.0004 ^c
Fresh frozen plasma	0.5 ± 1.0 (5)	2.4 ± 4.3 (13)	0.0012 ^c
Cryoprecipitate	0.3 ± 1.8 (1)	0.1 ± 0.3 (2)	NS

^a Values expressed as mean ± standard deviation; values in parentheses represent the number of patients requiring the product. ^b Reported previously from our group [33] in 30 consecutive patients having isolated coronary artery bypass grafting. ^c *p* Values of Fisher's exact test for the difference in number of patients requiring the products between the control and renal groups. The number of units of red cells, platelets, fresh frozen plasma, and cryoprecipitate are not significantly different between the two groups.

NS = not significant.

curred in a 60-year-old man who underwent urgent three-vessel CABG for unstable angina that required preoperative intravenous nitroglycerin. This patient died of sepsis secondary to acalculous gangrenous cholecystitis despite aggressive surgical treatment. There were 2 patients with a history of strokes who underwent urgent CABG, also for unstable angina. Both of these patients suffered a massive stroke in the postoperative period from which they became comatose and eventually died in the hospital after multiple infectious complications. The last death occurred in a patient who underwent aortic valve replacement, mitral valve replacement, and CABG for recurrent flash pulmonary edema while in the hospital. This patient did well for the first 10 postoperative days, then suffered an unexplainable cardiac arrest. Despite a successful resuscitation after this episode, his general condition progressively deteriorated and he finally died of sepsis after 3 months of hospitalization. All four deaths occurred in patients classified in NYHA class IV who underwent urgent operations (Table 4). Univariate analysis of the 22 perioperative variables followed by a stepwise logistic regression analysis revealed that preoperative NYHA class IV status and nonelective operations were independent predictors of operative mortality.

Comment

There is perhaps no other operative procedure that induces the enormous fluid shifts in the different body compartments as CPB procedures. The success of these demanding procedures depend partly on the ability of the kidneys to handle the rapid and voluminous fluid shifts in the perioperative period. In the absence of renal function, the tolerance of CPB is conceivably reduced. In addition to the immediate problems in the management of fluid and

electrolytes during CPB operations, the uremic patients also have a number of chronic conditions that predispose them to increased operative morbidity and mortality. These include their inability to excrete certain medications, bleeding diathesis secondary to coagulation defects and platelet dysfunction, and susceptibility to infection.

These potential problems explain the paucity of CPB procedures performed in dialysis patients until recently. In the early years of cardiac surgery, only sporadic cases were reported (Table 5). In the last 5 years, however, relatively larger series have been reported from the University of Alabama at Birmingham [27], University of Minnesota [28], Cleveland Clinic [29], University of Pennsylvania [30], Loyola University [31], and Mayo Clinic [32] with operative mortalities ranging from 3% to 16%. The increase in the number of reported cases in the recent years is likely related to the improved techniques in CPB and perioperative care. We now report an additional 25 cases performed during this period in our institution with an overall operative mortality of 16%. The discrepancies in the operative mortalities among these recent series are certainly related to other factors of comorbidity and the types and urgency of the operations. Taking all the reported cases that we managed to retrieve in the English-language literature since the advent of CPB, the overall operative mortality including the cases in the present study is 9% (see Table 5). The operative mortality of 7 patients in one series was not reported and therefore is not included in the calculation of the mortalities. The operative mortalities for the isolated CABG procedures, valvular operations, combined CABG with valvular operations, and thoracic aortic operations were 9% (20/236), 12% (6/47), 13% (1/8), and 0% (0/5), respectively. These data may serve as a guide in future decision making in the management of the chronically dialyzed patients.

Table 4. Operative Mortality

Variable	Mortality (%)
Operations	
CABG	3/16
AVR	0/3
AVR/MVR	0/1
AVR/CABG	0/1
AVR/MVR/CABG	1/2
MVR/CABG	0/1
TAAA	0/1
All operations	4/25 (16%)
Urgency	
Elective	0/13 (0%)
Nonelective	4/12 (33%)
NYHA classification ^a	
I-III	0/13 (0%)
IV	4/11 (36%)

^a Patient with TAAA repair not classified.

AVR = aortic valve replacement; CABG = coronary artery bypass grafting; MVR = mitral valve replacement; TAAA = thoracoabdominal aortic aneurysm repair.

Table 5. Literature Review of Cardiopulmonary Bypass Operations in Dialysis Patients

First Author	Year	Operations (deaths/cases)				Overall Operative Mortality	
		CABG	VR	Combined ^a	Aorta ^b	No.	%
Lansing [3]	1968	...	0/2	...	0/1	0/3	0
Ribot [4]	1971	...	0/1	...	...	0/1	0
Saldanha [5]	1972	...	0/1	...	...	0/1	0
Manhas [6]	1972	...	0/2	...	...	0/2	0
Haimov [2]	1973	...	2/4	...	...	2/4	50
Manzoian [7]	1974	0/1	...	...	...	0/1	0
Sakurai [8]	1974	0/1	...	...	...	0/1	0
Lansing [9]	1975	0/1	...	...	...	0/1	0
Lamberti [10]	1975	0/1	0/2	...	...	0/3	0
Posner [11]	1975	...	0/1	...	...	0/1	0
Wilcox [12]	1975	...	0/1	...	...	0/1	0
Kuehnel [13]	1976	0/6	...	...	...	0/6	0
Siegel [14]	1977	0/1	...	...	...	0/1	0
Crawford [15]	1977	0/2	...	...	...	0/2	0
Chawla [16]	1977	0/2	1/7	...	...	1/9	11
Lavelle [17]	1978	...	1/2	...	...	1/2	50
Soffer [18]	1979	...	0/1	...	...	0/1	0
Love [19]	1980	0/3	...	...	...	0/3	0
Francis [20] ^c	1980	1/8	...	0/2	...	1/10	10
Monson [21] ^c	1980	2/14	0/4	0/2	0/2	2/22	9
McGovern [22]	1984	0/1	0/1	...	...	0/2	0
Zamora [23] ^d	1986	7/6	7/1	...	...	?	
Laws [24]	1986	1/9	0/1	...	...	1/10	10
Marshall [25]	1986	1/12	...	...	...	1/12	8
Albert [26]	1987	0/11	0/2	...	...	0/13	0
Rostand [27]	1988	4/20	...	...	...	4/20	25
Opsahl [28]	1988	1/39	...	...	...	1/39	3
Peper [29]	1988	1/31	1/5	...	...	2/36	6
Deutsch [30]	1989	1/16	...	...	...	1/16	6
Blakeman [31]	1989	1/16	1/5	...	0/1	2/22	9
Batiuk [32]	1991	4/25	...	...	...	4/25	16
Current study	1993	3/16	0/4	1/4	0/1	4/25	16
Total						27/296	9

^a Combined CABG and VR. ^b Aortic operations. ^c May contain some of the same patients, as reports are from the same group. ^d Unclear mortality.

CABG = coronary artery bypass grafting; VR = valvular replacement.

The special management of uremic patients begins in the preoperative period. Some authors recommend dialysis more than 24 hours before the CPB procedure [9], whereas others recommend to have dialysis as close to the procedure as possible [6]. The argument for the former is to avoid hemodynamic instability that may arise immediately after dialysis, and the latter is to provide the most optimal fluid and electrolyte balance at the time of operation. In addition, one group advocated the use of intraoperative dialysis based on the experience of 1 case [18]. In our group, all patients were dialyzed the day before the operation by their usual route, hemodialysis or peritoneal dialysis. We have no experience of intraoperative dialysis and do not see its necessity. If not already present, a peritoneal dialysis catheter was always placed at the time of the operation under general anesthesia unless there

was a contraindication. Two patients had previous laparotomy, and the catheter could not be placed satisfactorily in 1 patient. Peritoneal dialysis was initiated immediately upon arrival to the intensive care unit to relieve the fluid load and to maintain a normal serum potassium level. The components of the dialysate and the rates of infusion and drainage were varied depending on the fluid and electrolyte status of the patient. Peritoneal dialysis was continued for the first 7 postoperative days, then switched to hemodialysis for those who were dependent on this mode of dialysis preoperatively. The catheter was removed before their hospital discharge for these patients. Antibiotic, usually first-generation cephalosporin, was routinely added to the peritoneal dialysate, and a sample of the drained fluid was cultured for organism daily as long as the catheter was in place.

The use of peritoneal dialysis has advantages over hemodialysis in the postoperative period. The administration of peritoneal dialysis is convenient with minimal equipment requirement and does not require a specialized technician. It can be initiated any time the surgeon deems it necessary without waiting for the dialysis team. Most importantly, it avoids the hemodynamic instability and the risk of heparin-associated bleeding associated with the use of hemodialysis; for these reasons, we have been able to begin dialysis immediately after operation.

The chronic anemia and bleeding tendency of the renal failure patients obligate them to a greater requirement of transfusion of blood products in the perioperative period of CPB operations that require full heparinization. Some authors recommend the use of preoperative red cell transfusion in this patient group because of their chronic anemia [10]. We routinely do not transfuse these patients preoperatively to elevate their normal level of red cell mass, in anticipation of the need for hemodilution during CPB. We do anticipate a greater need of red cell transfusion in the operating room and in the postoperative period. As demonstrated in Table 3, the blood product requirements of this group of renal patients were in fact greater than that of a cohort of elective patients with normal renal functions; a much greater proportion of the renal group needed red cell, platelet, and fresh frozen plasma transfusion than the control group. The greater number of units of red cell transfusion in the renal group was not due to greater mediastinal blood loss after sternal wound closure (see Table 3). The greater number of units of red cells used reflected more intraoperative usage, which was due to lower preoperative hematocrit levels and more intraoperative blood loss. Although as much of the blood loss that occurred in the operating room as possible was returned to the patient after a saline wash and centrifugation by the Cell Saver, a considerable amount of hemolysis can be expected from the negative pressure suctioning of pooled blood in the mediastinum and the processing in the Cell Saver. The hematocrit of these patients is usually kept greater than 0.24, as these patients are physiologically adjusted to chronic anemia.

The greater use of platelets and fresh frozen plasma again reflected the difficulty in achieving hemostasis after the discontinuation of CPB in the operating room. The renal patients have been shown to have platelet dysfunction and not so well characterized coagulation defects. Their platelets have been shown to have adhesion and aggregating deficiencies, and they have a factor III deficiency [34]. Although not routinely used, intraoperative platelet and fresh frozen plasma were much more frequently needed to achieve hemostasis before the sternal wounds were closed in these renal patients (see Table 3). Once hemostasis was deemed adequate, however, there did not appear to be greater postoperative blood loss in the first 24 hours. The use of these products at the end of the operation is always decided on by the operator without much objective data other than the activated clotting time and the amount of bleeding that is occurring at the time. Other coagulation studies and platelet counts require much time to perform and therefore would not be

useful in the operating room. We currently do not see an alternative to assess the coagulation status more accurately, which would theoretically minimize the use of blood products such as platelets, fresh frozen plasma, and cryoprecipitate.

Desmopressin acetate has been shown to decrease intraoperative and postoperative bleeding and transfusion requirements in patients undergoing "complex" or prolonged cardiac operations and also in patients who have an increased rate of mediastinal hemorrhage after CPB [35]. However, we were not able to show any benefits in postoperative mediastinal blood loss, transfusion requirement or platelet function by using desmopressin acetate in routine elective CABG cases [33]. We subsequently have discontinued its routine use in CPB surgery. The use of desmopressin acetate has been shown to improve bleeding time (a measure of platelet function) in uremic patients [36]. It would be interesting to determine if the routine use of desmopressin acetate after the discontinuation of CPB may reduce the requirement of blood products and mediastinal bleeding in the dialysis patients.

The most important electrolyte imbalance in CPB operations is that of potassium because elevated and reduced levels are associated with life-threatening arrhythmia, especially after ischemia. The sources of potassium during operation include tissue trauma from surgical manipulation, hemolysis from the bypass run, transfusion of red cells, and most notably the hyperkalemic cardioplegic solution. The concern of hyperkalemia from CPB operations, however, may be alleviated from the data shown in this study. There was in fact no correlation between the post-CPB serum potassium level and the amount of infused cardioplegic potassium, the length of bypass run, or the length of anesthesia time which would reflect the complexity or the degree of surgical trauma. On the contrary, there was a consistent and significant decrease in the serum potassium level as first measured postoperatively compared with the pre-CPB value; this was presumably caused by the process of hemodilution during CPB.

The renal failure patients are prone to infection, and this propensity is attributed to detectable leukocyte dysfunction in terms of chemotaxis and leukopenia [34]. In this series of 25 patients, there were only two incidents of minor postoperative infection and no sternal wound infection. Larger series will be needed to detect this potential problem. The patients in this group received perioperative prophylactic antibiotics as did other patients. The absence of renal function and the mode of dialysis at the time of administration need to be taken into account in the antibiotic doses as with all other medications.

A small but ever-present incidence of post-CPB gastrointestinal complications occurs with considerable hospital mortality as reported by our group [37, 38]. The incidence of intraabdominal ischemic viscus in this series appears high (2/25) as compared with that of the general cardiac surgery patient population in our institution [37]. It has been reported that accelerated atherosclerosis develops in renal failure patients on chronic dialysis [39]. It is plausi-

ble that the ischemic viscus was a consequence of a low flow state during CPB that was exacerbated by atherosclerotic mesenteric arteries in these patients. Perhaps higher bypass flow rates or higher perfusion bypass pressure may prevent this type of catastrophe.

The chronic arteriovenous fistulas of the renal patients are at risk for thrombosis in the operating room from applied pressure and perhaps during the low flow state. Six of 58 patients undergoing general surgical procedures in one series had this complication, and the authors of that series recommend using low-dose heparin solution infused into the fistulas [2]. This would not be necessary during CPB with full heparinization. We ensured that the arm with the fistula was well padded and did not have this particular complication.

Prophylactic pericardiectomy is recommended by two groups [16, 21] to prevent postoperative pericarditis, as this is already a common affliction of the renal patients. However, we have not employed this approach and have not had this complication in the renal patients. The use of aspirin has been shown to prolong aortocoronary graft patency [40], and this is routinely employed in our general cardiac surgery patient population. In light of the well-documented platelet dysfunction of the chronic renal patient [34], the risk/benefit ratio in the use of aspirin in this patient population is not clear. However, the pathogenesis of intimal hyperplasia and atherogenesis of bypass grafts involves the endothelium and possibly other cell types in addition to the platelets, and therefore it may be prudent to use aspirin also in the renal patients after CABG.

Two issues need to be addressed regarding valvular replacement in the dialysis patients. There is an obvious concern in the need for lifelong anticoagulation associated with the use of metallic valves in these patients who require frequent percutaneous puncture of their arteriovenous fistula for dialysis. However, there is some anecdotal evidence of premature calcification of tissue valves of these patients, presumably secondary to their imbalance in calcium metabolism [21]. For this reason, we routinely use metallic valves in the renal patients and place them on long-term anticoagulation. Furthermore, hemodialysis is definitely more invasive than dental and endoscopic procedures that normally require the use of prophylactic antibiotics. The need for long-term oral or intravenous antibiotics during hemodialysis on these patients with artificial valves is unclear and will require longer experience of considerably more patients.

Finally, the four operative deaths occurred in patients who were in NYHA class IV and who had urgent operations; these were shown statistically to be two independent predictors of operative mortality. However, the result of this statistical analysis should be viewed with considerable reservation. Three of the four deaths were not cardiac related. The death due to ongoing sepsis secondary to gangrenous cholecystitis was probably only avoidable if the diagnosis of cholecystitis was made earlier, and this was not related to the course of the patient's cardiac disease. There is no documented correlation between the urgency of CPB operation and gastrointestinal

complication. The sudden cardiac arrest that occurred in 1 patient at 5 AM of the 10th postoperative day after an uneventful postoperative course most likely was related to sudden arrhythmia. His ultimate death again was not likely related to the urgency of the operation or the stage of his cardiac disease. The 2 remaining patients who died of their massive postoperative strokes had a history of cerebrovascular disease. They were both operated on urgently. In these 2 cases, one can argue that if cardiac surgical intervention was considered electively earlier in the course of their cardiac diseases, perhaps their cerebrovascular disease could have been evaluated to the extent as to prevent the fatal complication. With the recent availability of color flow Doppler examination, bedside evaluation of the extracranial carotid arteries should be performed in the future even for the patients who are awaiting cardiac operation urgently.

In conclusion, this study demonstrated that elective CPB operations can be performed in chronic renal failure patients with excellent operative outcome when done with careful perioperative management. This requires a collaborative effort among the cardiac surgeon, anesthesiologist, nephrologist, and cardiologist, and significantly longer intensive care units and hospital stays should be expected. Nonelective cases and patients in the most advanced stage of their cardiac diseases had substantial operative mortality in this series. The overall operative mortality of the 296 cases reported in the English-language literature thus far is 9%, and this may serve as a guide in the consideration of surgical intervention of the dialysis patients with cardiac diseases. As shown in this study, the operative risks depend on the urgency of the operation and the stage of the disease. Only with considerably more experience can we better stratify the operative risks and benefits of the various CPB procedures for the renal failure patients with different cardiac diseases.

Batiuk and associates [32] have pointed out that coronary artery disease is responsible for 30% to 53% of deaths among chronic dialysis patients in the United States, Canada, Europe, Australia, and New Zealand. At the end of 1987, 98,400 patients were on chronic dialysis [34]. This number continues to increase because of the ever-improving technology in the mechanics of dialysis. In view of the high incidence of coronary artery disease of these patients with accelerated atherosclerosis, it is surprising that more patients are not referred to surgical intervention. The operative result of our group and the literature reviewed in this article is acceptable. We hope patients and their physicians will consider this option of therapy earlier in the course of the disease when the outcome of surgical intervention is most favorable.

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Surgical Experience With Defibrillator Implantation Using Nonthoracotomy Leads

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Between October 10, 1989, and June 17, 1991, 109 patients with life-threatening ventricular arrhythmias received an implantable cardioverter-defibrillator at our institution. In 50 patients, nonthoracotomy lead systems consisting of a subcutaneous chest wall patch electrode near the cardiac apex and one (Cardiac Pacemakers, Inc: Endotak C) or two (Medtronic: Transvene) transvenous electrodes were tested. The mean ejection fraction was 0.44 ± 0.15 with a range from 0.19 to 0.81. Twenty-four patients had a history of open heart operation. In 43 patients the nonthoracotomy lead system was implanted, whereas in 7 patients epicardial patch lead systems were required due to elevated defibrillation thresholds during nonthoracotomy lead testing. There was one perioperative death unrelated to the operative procedure (hydrocephalus

internus). Hemorrhage from the subcutaneous patch pocket or the device pocket that required reintervention occurred in 4 patients. During a mean follow-up of 13 ± 5 months (range, 4 to 26 months) no dislocation of an endocardial lead, insulation defect, or lead fracture has been observed. In 1 patient, the lead system had to be removed due to infection of the subcutaneous patch pocket. The cardiovascular survival rate was 98% at 12 and 18 months, and freedom from sudden cardiac death was 100% at 6 and 12 months. In conclusion, defibrillator implantation using nonthoracotomy lead systems is feasible with a success rate of 86%, and during short-term follow-up no problems related to the lead system such as dislocation, fracture, or insulation defect have occurred.

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The automatic implantable cardioverter-defibrillator (ICD) has been shown to be an effective tool in the treatment of drug-refractory sustained ventricular tachycardia/ventricular fibrillation and in survivors of sudden cardiac death who have a significant risk of recurrence. Mortality due to arrhythmias is greatly diminished in patients with ICDs. The reported incidence of sudden cardiac death at 1 year of follow-up in patients with the ICD is 1% to 4.6% [1-7]. Historical controls showed an incidence of recurrent sudden death in cardiac arrest survivors of 20% to 30% at 1- to 2-year follow-up [8, 9]. In view of these data, the ICD might be the first-line therapy of survivors of sudden cardiac death [10].

However, device and lead system insertion is associated with a defined morbidity and mortality, mainly related to any kind of thoracotomy that is required for placement of one or more defibrillation electrodes [1, 2, 5, 6, 11]. A number of complications that caused serious morbidity have been noted. The major problem encountered has been infection in 1% to 20% of the patients [1, 2, 5, 6, 11] with the necessity of explantation of the system. Other periprocedural complications include pneumonia, venous thrombosis, large pericardial and pleural effu-

sions, myocardial infarction, coronary artery laceration, and late constrictive pericarditis [12].

Defibrillator implantation in patients with a prior cardiac operation is complicated by periepicardial adhesions. Using a lateral thoracotomy and extrapericardial patch placement in combination with endocardial sensing leads may eliminate this difficulty in most cases. But in patients in whom the pleural space was opened during the prior operation (eg, after harvesting internal mammary artery grafts), difficulties caused by pleural adhesions may arise using this approach, and a higher incidence of pulmonary problems using this approach has been reported [5]. Patients with coronary artery disease who may require coronary artery bypass grafting in the future are at higher risk for perioperative complications during a later open heart procedure due to destruction of the epicardial landmarks. Thus, minimizing the implantation procedure—by avoiding thoracotomy—should lead to a reduction in morbidity and mortality.

The endocardial approach to internal defibrillation is not new. Hopps and Bigelow [13] did the first work on the concept of transvenous defibrillation. Mirowski, one of the inaugurators of ICD therapy, demonstrated the effectiveness of catheter defibrillation in the early 1970s [14]. Due to lower defibrillation thresholds, the most routinely used lead systems consisted of at least one epicardially or pericardially placed defibrillation patch electrode until recently. In 1987, the first nonthoracotomy lead system

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(Endotak; Cardiac Pacemakers, Inc [CPI], St. Paul, MN) was implanted in a small number of patients. Due to lead fractures during the follow-up, implantation was stopped to improve the leads [15-17]. A second transvenous lead system (model 6884 + 6881; Medtronic, Minneapolis, MN) was tested but not implanted in patients who received a defibrillator with epicardial lead placement in 1989 [18]. At our institution ICD implantation by transvenous subcutaneous approach was started in 1989, initially only in patients with a prior cardiac operation [19, 20].

The purpose of this report is to describe our initial surgical experience with two different nonthoracotomy lead systems in patients who underwent ICD implantation without concomitant open heart procedures.

Material and Methods

Patients

Between October 10, 1989, and June 17, 1991, 109 patients received an ICD at our institution. Approval by the local institutional human research committee has been obtained in August 1989. At the beginning only patients who had had a prior cardiac operation were selected for the nonthoracotomy approach. Before implantation, written informed consent was obtained. The patients had been informed that, in case of insufficient defibrillation by the endocardial approach, epicardial leads would be placed during the same procedure. In September 1990 after data were collected for 13 patients, our policy was changed and the nonthoracotomy approach was used as the method of first choice, except in patients who need concomitant open heart procedures.

Patient Evaluation

Patients were considered as candidates for defibrillator implantation if they had experienced at least one cardiac arrest caused by ventricular tachyarrhythmia or had recurrent sustained, life-threatening ventricular tachycardia. Before ICD implantation, each patient was evaluated with electrocardiography, Holter monitoring, maximal treadmill exercise testing, echocardiography, and left and right heart catheterization. Serial antiarrhythmic drug testing guided by electrophysiologic studies had failed to control ventricular arrhythmias in most patients or antiarrhythmic drug therapy had been withdrawn due to serious side effects of the drugs, and other therapeutic options such as map-guided antitachycardia operation or catheter ablation were not applicable or had failed in controlling the arrhythmias.

Lead Systems and Devices Implanted

Two different nonthoracotomy lead systems with their corresponding devices were implanted. The Medtronic nonthoracotomy lead system consisted of two transvenous leads and a subcutaneous patch electrode. The pulse generator (PCD model 7216A or 7217B; Medtronic) was a newly designed multiprogrammable, third-generation [21], automatic tachyarrhythmia control device. Defibrillation modalities available consisted of one

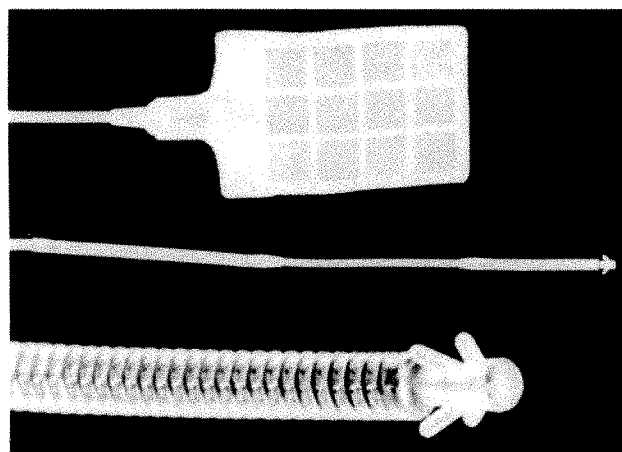


Fig 1. CPI Endotak C nonthoracotomy lead system: (top) subcutaneous patch electrode (Endotak SQ), (middle) transvenous lead with two defibrillation coils and the porous-tip electrode, (bottom) enlargement of the porous-tip electrode.

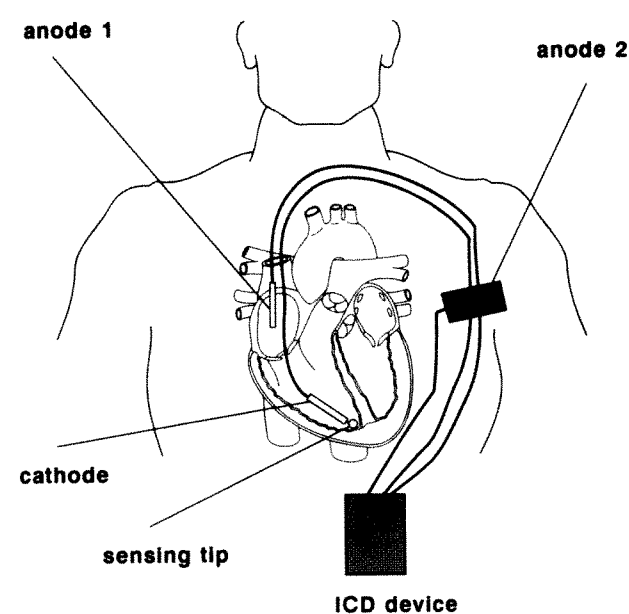
(single shock) or two (simultaneous or sequential) high voltage pulses. Two methods of overdrive pacing (burst and ramp) and cardioversion could be selected to terminate ventricular tachycardia. The CPI nonthoracotomy lead system was composed of one transvenous lead (Endotak C) and a subcutaneous patch lead (Fig 1). The pulse generator was a Ventak P 1550 programmable device (second-generation device) with options for cardioversion and defibrillation. The CPI Ventak PRx 1700 (third-generation device) was used instead of the Ventak P 1550 when available. The Endotak C lead has been manufactured with different distances between the right ventricular defibrillation cathode and the right atrial and superior vena caval anodes for use in patients with different sizes of right atria or ventricles.

Operative Procedure

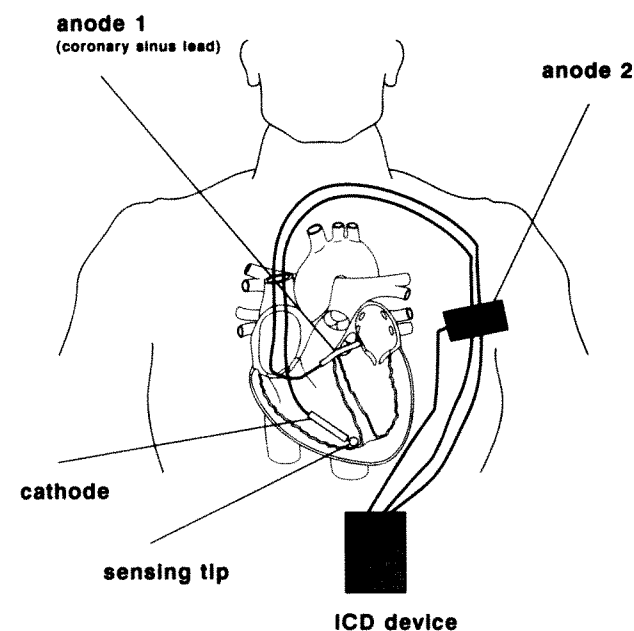
Implantation was done under general anesthesia. Before the surgical procedure, cutaneous self-adhesive electrodes were applied to the chest to defibrillate via an external direct-current defibrillator in case of insufficient internal defibrillation during the test procedure. The preparation of the operative field was done in such a manner that, in case of insufficient defibrillation by the nonthoracotomy leads, epicardial lead placement by a subxiphoid or transternal approach was possible.

Venous access was gained through a phlebotomy of the left cephalic vein or the left subclavian vein or by puncture of the subclavian vein using the Seldinger technique. The endocardial leads were positioned under fluoroscopic control.

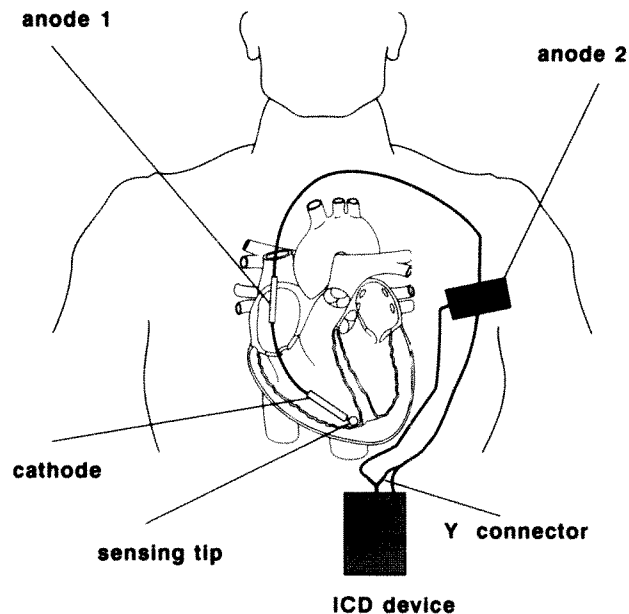
The Transvene (Medtronic) right ventricular electrode was a tripolar, endocardial screw-in lead. After positioning in the right ventricular apex the tip was actively fixed with its helical screw. Electrical measurements of pacing and sensing thresholds were performed. If the initial parameters were unacceptable, the ventricular lead was repositioned. The second transvenous lead was placed in



A



B



C

Fig 2. Nonthoracotomy lead systems. (A) Medtronic Transvene leads: second transvenous lead (anode 1) placed on the superior atriocaval junction. (B) Medtronic Transvene leads: second transvenous lead (anode 1) placed in the coronary sinus. (C) CPI Endotak leads: anode 1 and subcutaneous patch (anode 2) linked by a Y connector. (ICD = implantable cardioverter-defibrillator.)

the superior caval vein with its tip in the right atrium. In case of poor defibrillation threshold (DFT; minimal successful defibrillation energy ≥ 18 J) this lead could be positioned in the coronary sinus.

The Endotak C (CPI) lead, a porous-tip electrode, was also positioned in the apex of the right ventricle with fluoroscopic guidance. Passive anchoring was achieved by firmly wedging the tip into the trabeculae. Thereafter, pacing and sensing thresholds were determined.

The subcutaneous patch (Medtronic or CPI) was placed on the thoracic fascia near the cardiac apex by an incision in the anterior axillary line. To reduce impedance between patch and chest wall the patch pocket was filled with

isotonic saline solution and temporarily closed. Thereafter, the electrodes were connected to an external test device to measure the DFT.

After sufficient defibrillation had been achieved, a pulse generator pocket was created by a median incision in the epigastrium, the left rectus sheath was opened, and the rectus muscle was separated from the fascia behind until the dimension of the created space allowed tension-free placement of the device. The electrodes were connected to the device by subcutaneous tunnelling from the left delto-pectoral sulcus to the patch pouch incision and then together with the subcutaneous lead to the generator pocket (Fig 2). A final testing was done by telemetry when

Table 1. Electrophysiologic Testing Requirements

Variable	CPI Ventak PRx	Medtronic PCD
R-wave sensing		
Amplitude (mV)	>5	>5
Duration (ms)	<100	...
Slew rate (V/s)	...	>0.75
Pacing		
Threshold (V)	<1.5	<1.0
Impedance (Ω)	450-1200	250-800
Defibrillation		
Maximum DFT (J) (accepted)	20	18
Maximum energy (J) (delivered)	34	34

DFT = defibrillation threshold.

the electrodes were connected to the device. Drains were placed in the generator pocket and behind the subcutaneous patch electrode and the wounds were closed in layers.

Just before surgery and on the two following days all patients received intravenously antibiotics (cephamandol) as prophylactic treatment. After a short time of monitoring in the operation theatre, the patients were transferred to the cardiology ward with the device activated.

Intraoperative Electrophysiologic Testing

After proper positioning and anchoring of the right ventricular electrodes had been achieved, measurements of sensing and pacing characteristics were done. R-wave amplitudes greater than 5 mV, slew rates greater than 0.75 V/s, and pacing thresholds less than 1 V with a pulse width of 0.5 ms (impedance between 250 and 800 Ω) were accepted. Due to another arrhythmia detection algorithm, the requirements for the quality of the sensing signals had been less strict when using Ventak devices (Table 1). Instead of a slew rate criterion an R-wave duration in the recorded endocardial electrocardiogram (sensing leads) less than 100 ms was required. Although pacing was not

available in Ventak P 1550 devices, pacing threshold was measured in all patients to avoid problems if later the necessity of antitachycardia or antibradycardia pacing required an exchange of the device.

After the subcutaneous patch had been inserted and the connection of the leads with the external test device had been established, a low-voltage (100 V) synchronized shock was applied during sinus rhythm to ensure correct connections and to determine the resistance of the defibrillation leads. Resistances between 20 and 100 Ω were accepted. Ventricular fibrillation was induced by ramp pacing of the right ventricle or by alternating current (50 Hz).

The test protocols for the Transvene and Endotak leads differed slightly due to different functions of the devices and configurations of the lead system (Table 2). Using an external PCD pulse generator, a sequential shock with an energy of 18 J (550 V) between the right ventricular and the second transvenous electrode and between the right ventricular and the subcutaneous electrode was delivered. If the defibrillation was unsuccessful, a rescue shock was delivered by the external testing device (34 J) or by the external defibrillator with cutaneous patches.

As sequential shock delivery was not a feature of the CPI devices, the endocardial right atrial and subcutaneous electrode were linked by a Y connector. Testing was started with the same configuration as described above for the Medtronic lead system. After induction of ventricular fibrillation/flutter, a 20-J shock was delivered by an external device. If fibrillation continued an additional internal 40-J or an external 360-J rescue shock was delivered.

If the 20 J (Transvene, 18 J) shock was successful, ventricular fibrillation/flutter was defibrillated with decremental energies of 15, 10, and 5 J until the first failure occurred. At least three successes at 20 J or less [18] had to be achieved before the leads were implanted permanently. In case of failure with the first shock delivery configuration and as long as the patient showed no hemodynamic deterioration, several different lead configurations were tested. If no sufficient DFT was obtained with the nonthoracotomy leads, epicardial lead placement

Table 2. System Configuration

Variable	Medtronic	CPI
Sensing/pacing	True bipolar sensing electrode (tip of the RV lead)	Bipolar sensing between RV lead tip and defibrillation cathode
Anchoring	Active (helical screw)	Passive (porous tip)
Defibrillation	RV cathode, 2nd free positionable transvenous lead (SVC, CS)	RV cathode, 2nd, fixed distance transvenous lead (SVC, three distances available)
Patch electrode	Subcutaneous near cardiac apex	Subcutaneous near cardiac apex
Shock modality	Monophasic, sequential or simultaneous between (1) RV lead ² -patch and (2) RV lead-second transvenous lead (no fixed shock modality, current pathways programmable by telemetry)	Monophasic, simultaneous, selection of current pathways possible only during implantation by using a Y connector to establish the lead system

CS = coronary sinus; RV = right ventricular; SVC = superior vena cava.

Table 3. Synopsis of Patient Data

Patient No.	Sex	Age (y)	Diagnosis and Previous Operation	LVEF	NYHA Class	Device	Lead Configuration
1	M	66	3-VE CAD, ICM; CABG + MVR 10/86	0.23	III	PCD	RV/CS/SC
2	F	69	3-VE CAD, MI 11/89; CABG 10/89	0.60	II	PCD	RV/SVC/SC
3	M	57	3-VE CAD, MI; CABG + An	0.37	II	PCD	RV/SCV/SC
4	F	66	1-VE CAD, MI 79; An 79	0.35	III	PCD	RV/CS/SC
5	M	53	AVD; AVR 80	0.70	II	PCD	RV/SCV/SC
6	F	57	1-VE CAD, MI 89; An + ATO 1/90	0.31	II	PCD	RV/SCV/SC
7	F	22	TOF; Fallot correction 7/74	0.63	I	PCD	RV/SCV/SC
8	M	34	1-VE CAD, MI 89; An + ATO 1/90	0.30	III	PCD	RV/CS/SC
9	M	69	3-VE CAD, ICM; CABG 4/86	0.38	III	PCD	RV/SCV/SC
10	M	44	3-VE CAD; CABG 7/88	0.68	I	PCD	RV/SCV/SC
11	M	62	1-VE CAD, MI 88; An + ATO 5/90	0.36	II	PCD	RV/CS/SC
12	M	55	3-VE CAD; CABG 4/88	0.51	II	PCD	Epicardial sternotomy
13	M	58	DCM; none	0.40	III	Ventak P	RV/SCV + SC
14	M	55	2-VE CAD, MI 87; CABG 6/90	0.39	III	PCD	Epicardial, sternotomy
15	M	48	3-VE CAD; none	0.46	III	Ventak P	RV/SCV + SC
16	F	35	QT syndrome; none, hydrocephalus	0.77	I	Ventak P	RV/SCV + SC
17	M	57	3-VE CAD, ICM; none	0.23	I	PCD	Epicardial subxiphoidal
18	M	50	2-VE CAD; CABG 5/87	0.43	I	PCD	RV/SCV/SC
19	M	59	3-VE CAD, LV aneurysm; none	0.19	III	Ventak P	RV/SCV + SC
20	M	56	3-VE CAD, MI 89; CABG + MVR 3/90	0.28	III	PCD	RV/SCV/SC
21	M	50	DCM; none	0.43	II	Ventak P	RV/SCV + SC
22	M	63	CAD, LV aneurysm; none	0.41	I	PCD	RV/SCV/SC
23	M	60	3-VE CAD, MI 86; CABG 3/90	0.30	III	PCD	RV/SCV/SC
24	M	65	CAD, ICM; none	0.48	II	PCD	RV/SCV/SC
25	M	69	3-VE, CAD; CABG 7/88	0.57	III	Ventak P	RV/SC + SC
26	F	58	3-VE CAD, LV aneurysm; CABG + An 4/86	0.46	II	Ventak PRx	RV/SCV + SC
27	M	64	DCM; none	0.46	II	PCD	Epicardial sternotomy
28	M	38	DCM; none	0.29	II	Ventak PRx	RV/SCV + SC
29	M	54	3-VE CAD; CABG (+IMA graft) 7/86	0.44	II	Ventak PRx	RV/SCV + SC
30	M	67	DCM; none	0.37	III	Ventak P	RV/SCV + SC
31	M	17	AVRD; none	0.81	I	Ventak P	RV/SCV + SC
32	M	41	DCM; none	0.50	I	Ventak PRx	RV/SCV + SC
33	F	16	HNCM; none	0.48	I	PCD	RV/SCV/SC
34	M	65	3-VE CAD; CABG (+IMA graft) 3/88	0.34	III	PCD	RV/SCV/SC
35	F	64	AVRD; none	0.60	II	Ventak PRx	RV/SCV + SC
36	M	60	AVD + MVD; AVR + MVR 4/87	0.22	III	Ventak PRx	RV/SCV + SC
37	M	59	2-VE CAD; CABG 8/89, PTCA 2/91	0.40	II	PCD	RV/SCV/SC
38	M	47	1-VE CAD, AVD; CABG + AVR 3/90	0.47	II	PCD	RV/SCV/SC
39	M	69	3-VE CAD, ICM; none	0.34	III	Ventak PRx	RV/SCV + SC
40	M	50	2-VE CAD, MI; none	0.39	III	Ventak PRx	RV/SCV + SC
41	M	64	DCM; none	0.32	III	PCD	Epicardial sternotomy
42	M	34	2-VE CAD, PTCA 4/91; none	0.55	II	Ventak PRx	RV/SCV + SC
43	M	64	3-VE CAD, ICM; none	0.59	II	Ventak PRx	Epicardial subxiphoid
44	M	59	3-VE CAD, ICM; none	0.39	II	Ventak PRx	RV/SCV + SC
45	F	63	DCM; none	0.48	III	Ventak PRx	RV/SCV + SC
46	M	72	3-VE CAD; CABG 9/88	0.38	II	Ventak PRx	RV/SCV + SC
47	M	55	DCM; none	0.36	II	PCD	Epicardial subxiphoid
48	F	64	ARVD; none	0.78	I	PCD	RV/SCV/SC
49	M	70	3-VE CAD, ICM; none	0.37	I	PCD	RV/SCV/SC
50	M	53	2-VE CAD, LV aneurysm; none	0.38	II	Ventak PRx	RV/SCV + SC

An = aneurysmectomy; ATO = antitachycardia operation; AVD = aortic valve disease; AVR = aortic valve replacement; AVRD = arrhythmogenic right ventricle; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CS = coronary sinus; DCM = dilative cardiomyopathy; HNCM = hypertrophic nonobstructive cardiomyopathy; ICM = ischemic cardiomyopathy; IMA = internal mammary artery; LV = left ventricular; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MVR = mitral valve replacement; NYHA = New York Heart Association; PTCA = percutaneous transluminal coronary angioplasty; RV = right ventricular; SC = subcutaneous patch electrode; SCV = superior caval vein; TOF = tetralogy of Fallot; VE = vessel.

by a subxiphoid approach or by sternotomy was performed [22].

Postoperative Management and Follow-up

After removal of the drains, in the first 24 patients effective anticoagulation with heparin was started, which was followed by 6 months of coumarin therapy to prevent thrombus formation on the transvenous leads; the last 19 patients received low-dose heparin therapy followed by coumarin or aspirin for 6 months. Internal cardioverter-defibrillator energies for cardioversion/defibrillation were programmed to maximum values (Ventak P: 30 J; Ventak PRx, PCD: 34 J). Before hospital discharge and at regular intervals of at least 3 months the integrity of the leads was ensured by biplane chest roentgenogram and determination of sensitivity and pacing thresholds. Defibrillation was tested before hospital discharge and again after 2 (CPI) or 6 (Medtronic) months. The patients were advised to contact the outpatient clinic in any case of adverse reactions to the defibrillator, if they had noticed a defibrillation shock, or if syncope had occurred.

Data Collection and Statistical Analyses

All data are presented as the mean $\pm$ standard deviation, with range in parentheses. Life-table analysis was performed by the Kaplan-Meier method.

Results

Fifty patients participated in this study. Ten patients were women and 40 were men, with a mean age of 55 ± 13 years (range, 16 to 72 years). The underlying cardiac disease was coronary artery disease in 33 patients, dilative cardiomyopathy in 9 patients, hypertrophic cardiomyopathy in 1 patient, valvular heart disease in 2 patients, arrhythmogenic right ventricular disease in 3 patients, prolonged QT syndrome in 1 patient, and tetralogy of Fallot in 1 patient. The patients' clinical data are listed in Table 3. Mean ejection fraction, as determined from left ventricular angiography, was 0.44 ± 0.15 (range, 0.19 to 0.81). Ten patients were in New York Heart Association class I, 19 patients in class II, and 21 patients in class III. Twenty-four patients had previous open heart procedures. Among the 17 patients who had received coronary artery bypass grafting, 2 had patent internal mammary artery grafts. Other previous cardiac procedures are listed in Table 4.

During intraoperative testing ventricular fibrillation or flutter was induced an average of 6 ± 3 times to determine the DFTs. In 40 patients sufficient defibrillation (DFT ≤ 20 J [CPI] or 18 J [Medtronic]) was achieved by using the transvenous/subcutaneous approach with a mean DFT of 15 ± 4 J, whereas no optimal DFT with nonthoracotomy leads could be obtained in 10 patients. Nevertheless 3 patients with borderline DFTs (<25 J) received permanent implantation of a nonthoracotomy lead system due to some success at 18 J, no failures at 34 J, a prior cardiac operation, and administration of amiodarone at implantation. In the remaining 7 patients epicardial lead placement was done during the same procedure ($n = 5$) or

Table 4. Prior Cardiac Operations

Operation	No. of Patients
CABG	17
additional procedures	
AVR	1
MVR	2
Aneurysmectomy	2
Aneurysmectomy	4
additional procedures	
Antitachycardia operation	3
AVR	1
AVR + MVR	1
Fallot correction	1
Total	24

AVR = aortic valve replacement; MVR = mitral valve replacement.

during a second operation ($n = 2$) with a mean DFT of 16 ± 3 J (epicardial patches). Prolonged cardiopulmonary resuscitation for ventricular fibrillation due to temporarily insufficient defibrillation by internal and external electrodes was the reason for these two-stage procedures. Median sternotomy was used because of better exposure in case of a previous open heart operation (patients 12 and 18), failing defibrillation by subxiphoid approach (patient 41), or necessity of internal defibrillation by paddle electrodes (patient 27). In the other 3 patients a subxiphoid implantation was performed.

The operative procedure lasted 159 ± 63 minutes (range, 90 to 300 minutes). The seven implantations in which the nonthoracotomy approach failed lasted 208 ± 48 minutes (range, 160 to 300 minutes) (in case of two-stage procedures, both operation times were added). The creation of the patch and device pockets were done after achieving sufficient pace/sense thresholds (patch) and defibrillation thresholds (device) early in our experience. During the last 20 procedures, testing and preparation were performed simultaneously to shorten the procedure. The last 10 procedures were performed with a mean operative time of 117 ± 26 minutes.

No intraoperative complications occurred. Postoperatively, there was one death unrelated to the procedure (patient 16) caused by a hydrocephalus internus with consecutive brain death on postoperative day 6. Hemorrhage that required reintervention occurred in 4 patients. Bleeding from an epigastric vessel was the reason for a revision of a device pocket. In another case of patch pocket hematoma, no circumscribed bleeding was found. Two reinterventions were required because of patch pocket hematomas on the eighth day immediately after shock delivery during predischARGE testing (patient 48) and in the sixth week (patient 38) after an initially uneventful postoperative course. In both patients bleeding from chest wall arteries was found. Late infection of the subcutaneous patch pocket occurred in 1 patient (patient 8). In this patient, removal of the whole system was performed without any problem 7 months after implan-

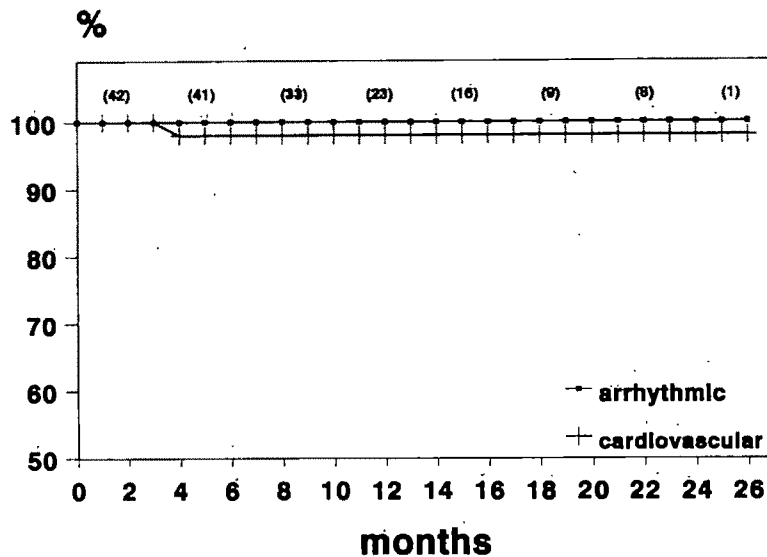


Fig 3. Kaplan-Meier survival curves for patients with nonthoracotomy lead systems. Numbers above points indicate the number of patients available for analysis. (Arrhythmic survival = freedom from sudden cardiac death.)

tation. The endocardial leads were easily withdrawn. Thrombosis of the subclavian vein developed in 1 patient 1 month after implantation. One patient died 4 months after implantation due to progressive heart failure.

There has been no dislocation of an endocardial lead, and pacing and sensing function is proper in all patients but 1. In this patient pacing threshold increased to a level close to exit block (1.04 ms at 5.4 V) while sensing function was not altered. During follow-up, stability of the lead system was 100% at 12 and 18 months.

In all patients ventricular fibrillation/flutter induced at the pre-discharge or follow-up tests was terminated successfully by the ICD. Twenty-two of 43 patients (51%) experienced cardioversion/defibrillation because of spontaneous ventricular fibrillation/flutter episodes 3.4 ± 4 months after implantation. Life-table analysis (Fig 3) indicated 12- and 18-month cardiovascular survival of 98% and a freedom from sudden cardiac death of 100% at 6 and 12 months.

Comment

Our study indicates the practicability of nonthoracotomy lead systems in all patients who need an ICD device without a concomitant open heart operation. Using nonthoracotomy lead systems, an intraoperative defibrillation threshold lower than or equal to 20 J showed a reliable function of the implanted defibrillation device during follow-up.

Forty of our 50 patients who entered the study fulfilled this criterion. Three borderline cases ($20 \text{ J} < \text{DFT} < 25 \text{ J}$) were included due to the fact that all 3 patients received amiodarone during implantation and reduction of the DFT after discontinuation of amiodarone was foreseeable [2, 23]. Thus we conclude that about 86% of ICD implantations without concomitant open heart procedures could be performed with nonthoracotomy lead systems. Studies to predict an insufficient DFT and investigations to improve the effectiveness of this approach are in progress.

Our own experience indicates that the use of amiodarone and low ejection fraction are risk factors for an insufficient DFT and that biphasic shocks will improve DFTs. The mean ejection fraction in our series is higher than in other reported series. One reason may be the inclusion of 4 patients with normal left heart function (3 patients with arrhythmogenic right ventricle and 1 with QT syndrome) in this study.

The advantages of this new technique are evident: due to the minor surgical procedure all patients were extubated at the end of the operation or in the recovery room. Mobilization of the patients was attainable early; in our series all patients were completely mobilized until the second postoperative day. No postoperative pneumonia, which was a serious complication in other series [5], occurred in these patients. Complications such as pericardial or pleural effusions and coronary vessel laceration, which have been observed with thoracotomy and epicardial lead insertion, did not occur after transvenous/subcutaneous lead placement. In patients with coronary artery disease and the probability of future coronary artery bypass grafting (eg, patient 42), difficulties caused by obliteration of epicardial landmarks were avoided [24]. As with all foreign body implantations, infection causes serious problems. Removal of the whole ICD system is required for definitive cure. An incidence of infection of 1% to 20% has been described for epicardial defibrillators. In our series infection occurred in 1 patient (2%), but in contrast to conventional ICD patches, the endocardial and subcutaneous electrodes were easily withdrawn by a minor surgical procedure. Bleeding from the device and the subcutaneous patch pouch was a complication that required reintervention in 4 patients. During the study we have learned that the side branches of the thoracodorsal artery have to be dissected carefully and that no vessels should be left in place between the chest wall muscles and the subcutaneous patch electrode. After paying attention to this point and changing the anticoagulation therapy

(low-dose heparin therapy except in patients with artificial valves), we seem to have solved this problem.

Seven patients in whom nonthoracotomy lead systems did not work received an epicardial patch electrode system, which worked with proper defibrillation thresholds. Prolonged duration of the surgical procedure or the need for a second operation and discomfort by the additional wounds are major disadvantages for these patients. During our study, we have learned to use the sensing capability of the transvenous electrodes in combination with the epicardial patches. This procedure promises better sensing and pacing values and avoids placement of epicardial sensing leads in cases of failed defibrillation by the nonthoracotomy lead system. Thus, this subgroup may also benefit from the placement of nonthoracotomy leads.

Postimplantation failure of the endocardial lead system is a further critical topic to discuss. Dislocation of the right ventricular lead, lead fractures, and insulation defects are of surgical interest. Sensing problems that cause inappropriate shocks during normal rhythm or failure to deliver appropriate therapy are well-known problems in epicardial defibrillation therapy [2, 3, 5, 25]. Insufficient defibrillation shocks due to increased defibrillation thresholds in the follow-up period are also serious complications. In 1988 a small series of Endotak C leads was implanted. The investigation was terminated due to lead fractures and related sudden cardiac deaths [26].

By using the improved CPI and Medtronic leads we have not monitored any lead dislocation, lead fracture, or insulation defect. All implanted systems are working without major problems, and arrhythmic survival has been excellent during a mean follow-up of 13 ± 5 months while arrhythmic events have not been rare. Inappropriate shocks or missing shocks caused by sensing problems have not occurred. The use of endocardial instead of epicardial sensing electrodes may be a possible explanation, as the superiority of endocardial electrodes has been established by bradycardia pacemaker experience [27, 28]. The patient with a PCD pulse generator in whom an increased pacing threshold was monitored during follow-up was not dependent on VVI pacing. As a threshold of 1.04 ms at 5.4 V was monitored, the output of the PCD was set at maximum (1.59 ms at 5.4 V) for reliable antitachycardia pacing. Only permanent VVI pacing at these settings will have a significant negative impact on longevity of the battery; therefore, the patient did not need a revision of the right ventricular lead.

The intention of implanting nonthoracotomy lead systems instead of epicardial leads was a reduction in perioperative morbidity and mortality at the cost of a slight elevation in the DFTs compared with patch lead systems. Our present data cannot demonstrate a significant reduction in mortality or morbidity. The overall complication rate of 14% in this series compares well with epicardial procedures. But, due to the growing experience with the nonthoracotomy lead systems, there is an improvement in the implantation procedure, which leads to a reduction in periprocedural complications. Technical improvements such as biphasic shocks, reduction of the size of the

devices, and a new design of the chest wall electrode will simplify the procedure. In February 1992 the 100th nonthoracotomy implantation was done at our institution, and hopefully we can demonstrate a significant reduction in perioperative morbidity in this greater series after collection of the short-term follow-up data. Up to the time of this report, our short-term follow-up has demonstrated the stability of the nonthoracotomy lead systems and has uncovered no failure of the defibrillation function. A definitive evaluation of the defibrillation capability with the nonthoracotomy lead systems is reserved until the completion of long-term follow-up.

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Calprotectin and Complement Activation During Major Operations With or Without Cardiopulmonary Bypass

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Plasma concentrations of the granulocyte cell marker calprotectin were assessed during operation and 24 hours postoperatively in patients undergoing coronary artery bypass grafting with cardiopulmonary bypass, abdominal aneurysmectomy with implantation of an aortic graft, or thoracotomy without implantation of synthetic material. The concentration of calprotectin increased significantly ($p < 0.01$) in all three groups. Ten of the 30 patients in the group undergoing cardiopulmonary bypass received methylprednisolone at the start of the operation. No difference in calprotectin concentration was seen between the two subgroups ($p > 0.05$). Plasma concentration of calprotectin was shown to increase rapidly in patients undergoing cardiopulmonary bypass and

aneurysmectomy, in whom complement activation also took place. However, the calprotectin concentration increased slowly during the operation and the postoperative period in patients undergoing a thoracotomy, in whom complement was not activated. At wound closure the calprotectin concentration was significantly elevated in the cardiopulmonary bypass and aneurysmectomy groups compared with the thoracotomy group ($p < 0.05$). The calprotectin concentration remained elevated during the postoperative period in all three groups. Our results indicate that calprotectin may serve as a suitable cellular marker when the biocompatibility of artificial surfaces is studied.

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Complement activation occurs when blood is exposed to artificial material during extracorporeal circulation as in cardiopulmonary bypass (CPB) and hemodialysis [1]. Activation of the complement system leads to the generation of many biologically active fragments. The potent anaphylatoxin C5a may cause activation and accumulation of polymorphonuclear neutrophils (PMNs).

A transient leukopenia occurs during CPB and hemodialysis as a result of PMNs being removed from the circulation and sequestered in the lungs [2, 3]. This phenomenon is suggested to be caused mainly by the generation of C5a [4].

The calprotectin (L1) molecule is a major neutrophil cytoplasmic protein and is found both in squamous epithelial cells and monocytes but is absent in lymphocytes [5, 6]. Although its function *in vivo* is presently unknown, it has recently been shown that calprotectin has antibiotic properties and may be fungicidal and bactericidal *in vitro* [7].

Elevated plasma levels of calprotectin have been observed in patients with infections and various inflammatory diseases [8, 9]. Calprotectin is released from the cells upon activation and cell death and may thus be a useful marker of PMN activity [10, 11].

Recently calprotectin has been shown to be released during CPB [12]. In the present study the release of calprotectin during major operations with and without CPB was monitored and compared with the previously reported changes in complement activation occurring during these procedures [13, 14].

Patients and Methods

The study was performed on blood samples from patients previously described [13, 14]. Thirty patients (25 men and 5 women) underwent elective coronary artery bypass grafting. Seven patients (all men) underwent abdominal aneurysmectomy with implantation of an aortic woven Dacron graft, and 5 patients (3 men and 2 women) underwent a thoracotomy without implantation of synthetic material. In the coronary artery group 10 patients received methylprednisolone (30 mg/kg body weight) intravenously immediately before the start of CPB. The median age in the CPB group was 57 years (range, 35 to 68 years). The median age in the aneurysmectomy group was 68 years (range, 54 to 77 years), and in the thoracotomy group, 56 years (range, 41 to 69 years). The age difference among the groups was not statistically significant. No differences in operation time (169 minutes; range, 97 to 285 minutes) or duration of CPB (70 minutes; range, 29 to 128 minutes) were observed between the two CPB groups. Aortic cross-clamping was initiated in the

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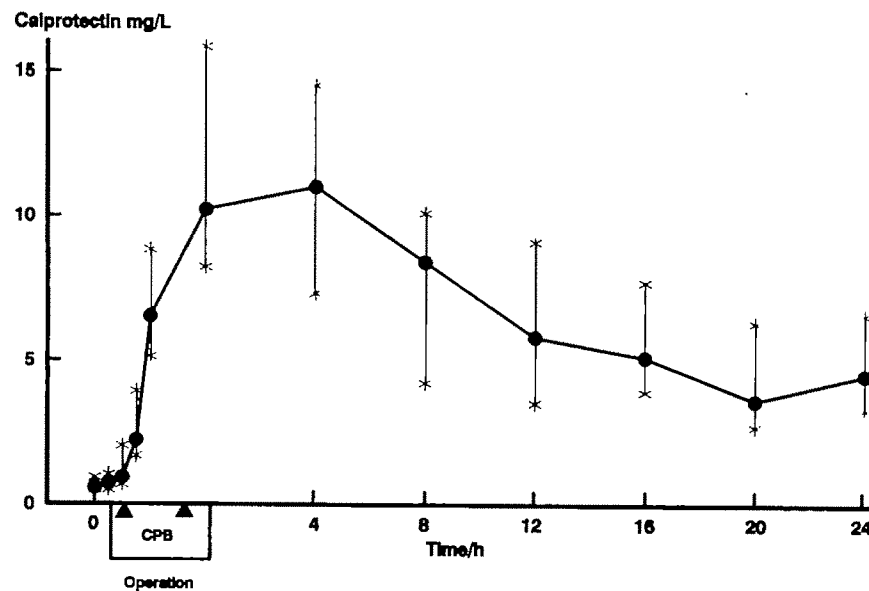


Fig 1. Plasma concentration of calprotectin in 20 patients undergoing coronary artery bypass grafting with cardiopulmonary bypass (CPB). Median values and interquartile range are shown.

aneurysmectomy group 75 minutes (range, 51 to 126 minutes) after the start of the operation. The median aortic cross-clamping time was 71 minutes (range, 49 to 115 minutes).

Anesthesia was performed according to a standard procedure including thiopental sodium, diazepam, fentanyl, pancuronium, and nitrous oxide.

For CPB a polystan VT 11500 bubble oxygenator connected to a 2,000-mL cardiectomy reservoir (Polystan, Copenhagen, Denmark) and an HF-6000 Swank arterial filter (Pioneer Viggo Inc, Beaverton, OR) were used in all patients. The extracorporeal circuit was primed with 500 mL of dextran in sodium chloride (0.9%), 500 mL of Ringer's acetate, 500 mL of glucose (5%), 500 mL of mannitol (15%), and 250 mL of carbonic acid (4.2%) (500 mmol/L).

Blood samples were drawn from the left radial artery before anesthesia and at the start of the operation. In the CPB group blood samples were drawn when CPB was established and then 30 minutes and 60 minutes after the start of CPB. In the other groups corresponding samples were obtained 1 hour after the start of the operation and 30 and 60 minutes later. In all patients additional samples were drawn at wound closure and every 4 hours for 24 hours.

Blood samples were collected into tubes containing ethylenediaminetetraacetic acid and immediately stored on ice. The samples were centrifuged within the next 3 hours, and the plasma was stored at -70°C until testing.

In each sample the number of white blood cells and the hemoglobin concentration were determined in an electronic counter (Coulter Electronics Ltd, Harkenden, UK). Blood smears were stained with May-Grünwald Giemsa stain and incubated with α -naphthyl acetate for demonstration of nonspecific esterase activity.

Plasma calprotectin level was determined by a double antibody enzyme immunoassay [15]. In brief, polystyrene plates were coated with a polyclonal rabbit anti-

calprotectin antibody. Standards and samples were incubated at room temperature. The second antibody was a polyclonal rat anti-calprotectin antibody. The detection antibody was alkaline phosphatase conjugated rabbit anti-rat immunoglobulin. *P*-nitrophenyl phosphate was used as substrate. Within assay precision was calculated to be 1.9% and between assay precision 14.8%. Lower detection limit was found to be $1.0\ \mu\text{g/L}$. The normal plasma level for calprotectin is 0.08 to 0.80 mg/L for women and 0.15 to 0.91 mg/L for men.

The PMN counts and plasma C3dg and plasma terminal complement complex (TCC) concentrations have previously been reported [13, 14].

Cell counts and concentrations of complement activation products and calprotectin were corrected for hemodilution according to the formula:

$$\frac{\text{Sample concentration} \times \text{initial hemoglobin}}{\text{Sample hemoglobin}}$$

All data are given as median values with interquartile range. The Friedman test was applied for comparison of samples drawn at different times within each group. Values were compared with baseline. The Kruskal-Wallis test was used for comparisons between the various groups and was examined at wound closure and 24 hours postoperatively. Values of *p* less than 0.05 were considered significant (two-tailed test).

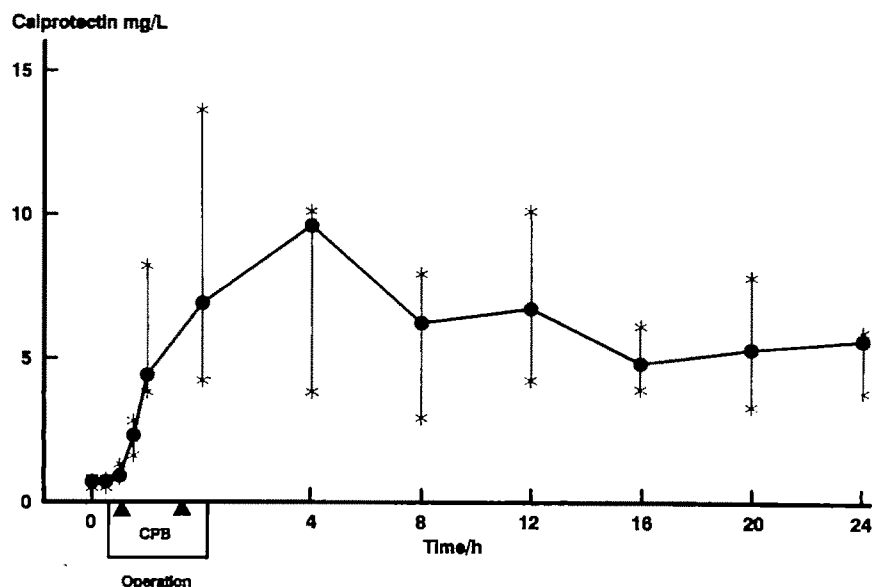
The study was approved by the ethical committee of Ullevaal Hospital, and informed consent was obtained from each patient.

Results

Plasma Calprotectin

During CPB in the nonsteroid subgroup the calprotectin concentration increased from a baseline value of 0.5 mg/L (range, 0.5 to 0.9 mg/L) to a maximum of 11 mg/L (range,

Fig 2. Plasma concentration of calprotectin in 10 patients undergoing coronary artery bypass grafting and given methylprednisolone (30 mg/kg body weight) immediately before cardiopulmonary bypass (CPB). Median values and interquartile range are shown.



7.3 to 14.5 mg/L) 4 hours postoperatively ($p < 0.01$) (Fig 1). In the steroid subgroup the calprotectin concentration likewise reached a peak of 9.6 mg/L (range, 3.8 to 10.1 mg/L) 4 hours after the operation ($p < 0.01$) (Fig 2). After the initial peak the concentration of calprotectin gradually decreased to 4.5 mg/L (range, 3.3 to 6.6 mg/L) in the nonsteroid subgroup and to 5.6 mg/L (range, 3.8 to 5.9 mg/L) in the steroid subgroup 24 hours after the operation. However, the concentration remained markedly elevated compared with baseline ($p < 0.01$). The two subgroups did not differ significantly with regard to concentration of calprotectin in plasma ($p > 0.05$).

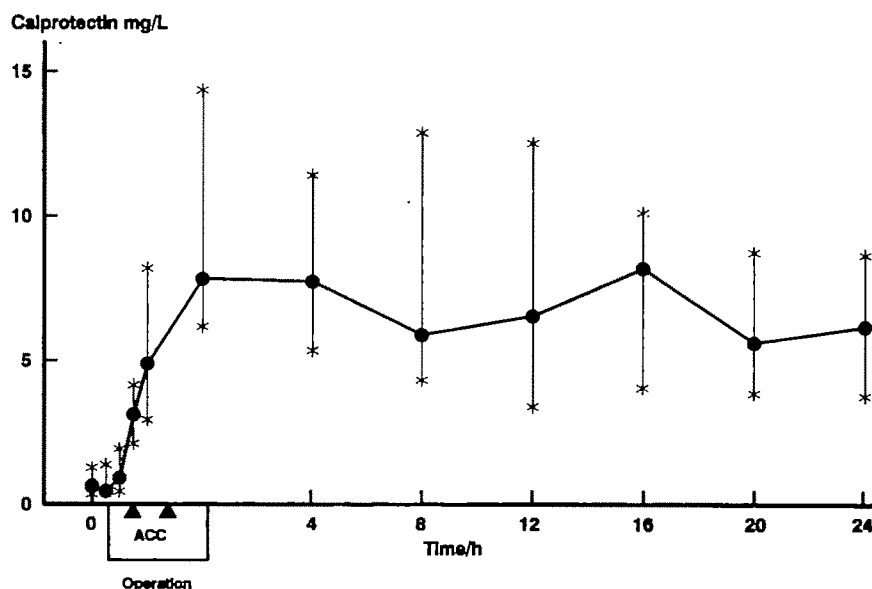
In the aneurysmectomy group the calprotectin concentration was 0.7 mg/L (range, 0.4 to 1.4 mg/L) before the operation. An increase in calprotectin concentration was seen after aortic cross-clamping was initiated and contin-

ued to rise after release of the clamp to 8.5 mg/L (range, 6.7 to 15.6 mg/L) at wound closure ($p < 0.02$). Then the calprotectin concentration gradually decreased to 6.7 mg/L (range, 4.1 to 9.4 mg/L) 24 hours after the operation (Fig 3). The concentration remained markedly elevated, however, compared with baseline ($p < 0.01$).

In the thoracotomy group the calprotectin concentration increased from 0.6 mg/L (range, 0.4 to 1 mg/L) before the operation to 6.1 mg/L (range, 3.8 to 10.2 mg/L) 8 hours after the operation ($p < 0.05$) (Fig 4). The calprotectin concentration remained elevated during the rest of the study period.

At wound closure the concentration of calprotectin was significantly elevated in the CPB and aneurysmectomy groups compared with the thoracotomy group ($p < 0.05$). Twenty-four hours after the operation no significant dif-

Fig 3. Plasma concentration of calprotectin in 7 patients undergoing aneurysmectomy and implantation of an aortic graft. Aortic cross-clamping (ACC) time is indicated. Median values and interquartile range are shown.



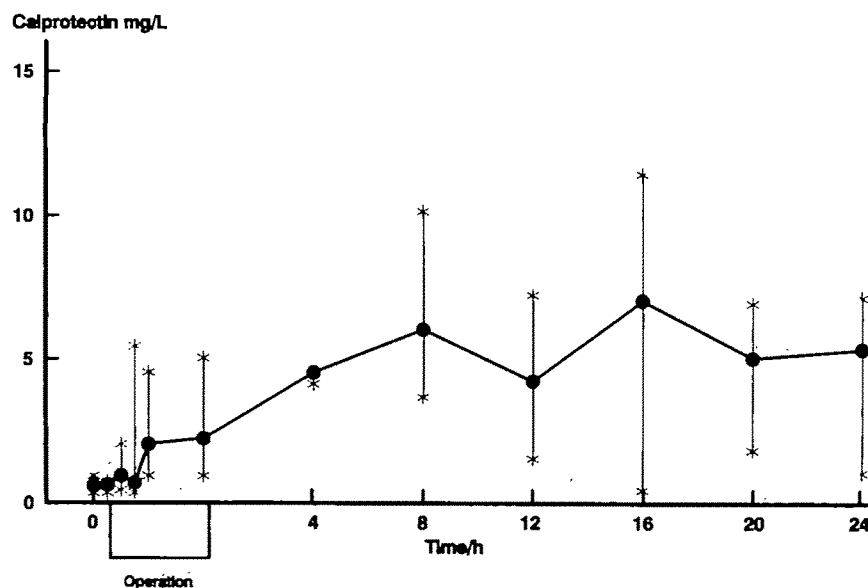


Fig 4. Plasma concentration of calprotectin in 5 patients undergoing thoracotomy without the implantation of synthetic material into the circulation. Median values and interquartile range are shown.

ference in calprotectin concentration was found between the groups ($p > 0.05$).

Plasma C3dg

As previously reported [13, 14], during CPB in the non-steroid subgroup (Fig 5) and in the steroid subgroup (data not shown) the C3dg concentration reached a peak value 4 hours after the operation and at wound closure, respectively, and then gradually decreased toward baseline during the observation period. The two subgroups did not differ significantly in regard to concentration of C3dg in plasma. In the aneurysmectomy group the changes in C3dg concentration were almost identical to observations in the CPB group (Fig 6). In the thoracotomy group the C3dg concentration remained unchanged during the observation period (Fig 7).

Plasma Terminal Complement Complex

As previously reported [13, 14], during CPB in the non-steroid subgroup (see Fig 5) and the steroid subgroup

(data not shown) the TCC concentration reached a peak value after 1 hour. Four hours postoperatively the TCC concentration had decreased almost to baseline. In the aneurysmectomy and thoracotomy groups no changes in TCC concentrations were observed (see Figs 6, 7).

Polymorphonuclear Neutrophils

As previously reported [13, 14], after 30 minutes of CPB there was a significant decrease in PMN count in both the nonsteroid subgroup (see Fig 5) and the steroid subgroup (data not shown), with no significant intergroup difference. However, in the postoperative period a significant difference was observed. In the nonsteroid subgroup a maximum was reached 8 hours after the operation, whereas in the steroid group the PMN count gradually increased during the observation period. At 12 hours and throughout the study the PMN count was significantly higher in the steroid subgroup than in the nonsteroid subgroup. In the aneurysmectomy group the number of PMNs increased steadily after the start of the operation,

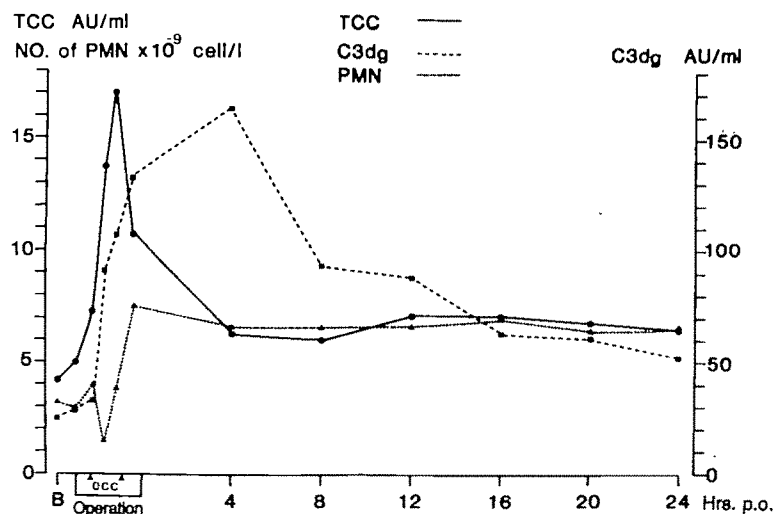
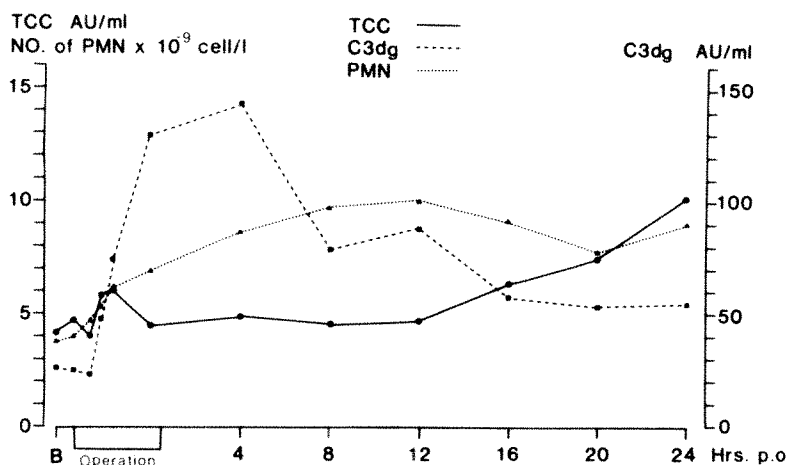


Fig 5. Plasma concentration of C3dg, terminal complement complex (TCC), and polymorphonuclear neutrophils (PMN) in patients undergoing coronary artery surgery with cardiopulmonary bypass. (ecc = extracorporeal circulation.) (Reprinted from Fosse E, Mollnes TE, Ingvaldsen B. *J Thorac Cardiovasc Surg* 1987;93:860-6, with permission.)

Fig 6. Plasma concentration of C3dg, terminal complement complex (TCC), and polymorphonuclear neutrophils (PMN) in patients undergoing aneurysmectomy and implantation of an aortic graft. (Reprinted from Fosse E, Mollnes TE, Ingvaldsen B. *J Thorac Cardiovasc Surg* 1987;93:860-6, with permission.)



reaching a peak 12 hours postoperatively (see Fig 6). The number of PMNs remained elevated during the observation period. In the thoracotomy group a gradual increase in PMNs was observed after the start of the operation to a maximum at 24 hours postoperatively (see Fig 7).

Comment

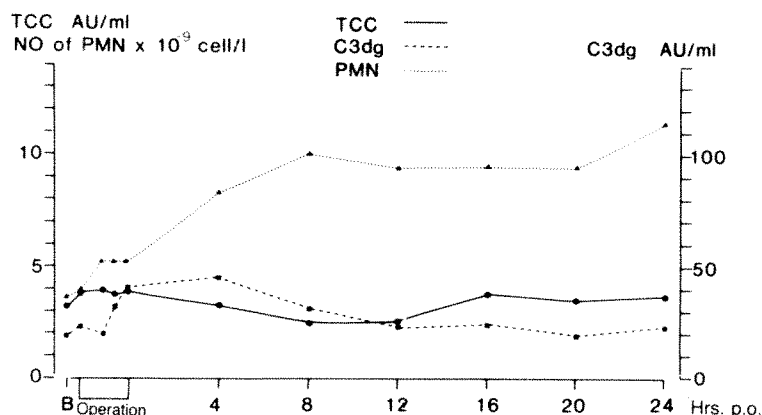
This investigation shows that calprotectin is released from PMNs during major operations with or without extracorporeal circulation. The release of calprotectin at the start of CPB coincided with the increase in C3dg and TCC levels and the transient decrease in PMN count. In the aneurysmectomy group the increase in calprotectin level corresponded with the increase in C3dg level that was seen when aortic cross-clamping was initiated. Aortic cross-clamping has previously been shown to induce complement activation [16]. After unclamping, when the blood came in contact with the implanted aortic Dacron graft the concentration of calprotectin and C3dg continued to increase. At wound closure we observed that the calprotectin concentration was significantly elevated in the CPB and the aneurysmectomy groups compared with the thoracotomy group. However, postoperatively no difference in the calprotectin concentration was observed. This implies that blood contact with artificial surfaces may

induce release of calprotectin. The actual release of calprotectin may have been underestimated during coronary artery bypass grafting because the CPB circuit itself may adsorb circulating proteins [17]. Our results suggest that calprotectin is a suitable marker for leukocyte activation when blood is exposed to synthetic materials. More conclusive information, however, may be obtained from the in vitro biocompatibility model developed by Videm and associates [18, 19].

C3dg and TCC are recognized as appropriate indicators of complement activation. This is in contrast to measurement of C5a due to the short plasma half-life of this molecule [13]. Because C5a is known to induce PMN aggregation, sequestration, and activation [20], it is tempting to speculate that the initial release of calprotectin during CPB and aneurysmectomy is caused by complement activation. In vitro studies have shown that binding of C5a to PMNs provokes the cells to release the content of the primary and secondary granules [21]. Moreover, the hypothesis that release of PMN granular contents in vivo is complement-dependent is supported by studies that have shown increased plasma levels of elastase and lactoferrin during hemodialysis [22, 23].

In both the CPB and the aneurysmectomy groups the C3dg concentration returned almost to baseline after the operation. In contrast, the calprotectin concentration re-

Fig 7. Plasma concentration of C3dg, terminal complement complex (TCC) and polymorphonuclear neutrophils (PMN) in patients undergoing thoracotomy. (Reprinted from Fosse E, Mollnes TE, Ingvaldsen B. *J Thorac Cardiovasc Surg* 1987;93:860-6, with permission.)



mained elevated in the postoperative period. This may partially be due to the previously described elevation of calprotectin level seen during inflammation and tissue repair [8, 9]. Our observations from the thoracotomy group support this view because the calprotectin concentration increased slowly during the postoperative period even if no complement activation was observed. Thus, additional mediators besides complement may induce calprotectin release.

Administration of methylprednisolone before CPB affected neither the generation of calprotectin nor the generation of complement activation products. This is an interesting observation because the PMN count increased significantly more in the steroid group than in the non-steroid group. Moreover, treatment with corticosteroids is known to modulate PMN responses in general [20, 24].

The clinical significance of calprotectin measurements is still obscure. However, the recent findings that calprotectin has a significant antibacterial effect and is released in response to endotoxins indicate that the molecule may have important in vivo functions [7, 10].

In conclusion, our results show that the initial release of calprotectin seen during CPB and aneurysmectomy coincided with the activation of the complement system. The antimicrobial effect of calprotectin and its presence in PMNs and macrophages may further link the complement system to cellular host defense mechanisms. Moreover, calprotectin may serve as an appropriate cellular indicator when the biocompatibility of artificial surfaces is studied.

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Effects of Pressure and Duration of Hyperkalemic Infusions on Endothelial Function

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Infusions of crystalloid hyperkalemic cardioplegic solutions (CHCSs) are known to impair endothelium-dependent coronary relaxation. This impairment might also be influenced by high perfusion pressure and duration of CHCS infusion. To verify this hypothesis, we designed experiments to study the influence of pressure and duration of CHCS infusion as modulating factors in CHCS-related endothelial impairment. Isolated hearts of Sprague-Dawley rats were studied in a Langendorff apparatus for coronary endothelial function. Hearts ($n = 6$) were exposed to four different CHCSs containing 12, 24, 40, or 100 mmol/L of potassium chloride (KCl). Endothelial and smooth muscle functions were respectively tested by infusion of 5-hydroxytryptamine (1×10^{-6} mol/L) and sodium nitroprusside (1×10^{-5} mol/L) before and after CHCS perfusion. In group I ($n = 24$),

37°C CHCSs were perfused at 80 cm H₂O of pressure for 30 minutes. In group II ($n = 24$), the same CHCSs were perfused at 160 cm H₂O for 30 minutes. In group III ($n = 18$), CHCSs containing 24, 40, and 100 mmol/L of KCl were infused at 160 cm H₂O for 10 minutes. In all groups, response to sodium nitroprusside was unaltered by CHCS infusion, indicating that smooth muscle function was preserved. However, in group II, 5-hydroxytryptamine-induced vasodilatation was significantly impaired in hearts perfused with CHCS containing 24 mmol/L of KCl or more, suggesting endothelial damage. This study demonstrates that, in addition to KCl concentration, pressure and duration of infusion are two major determinants in CHCS-mediated endothelial damage.

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Crystalloid hyperkalemic cardioplegic solutions (CHCSs) are currently used to optimize myocardial protection during open heart operations [1, 2]. The principle common to all these solutions is the rapid induction of diastolic myocardial arrest due to their high potassium content. Although hyperkalemia itself has not been reported to be harmful to myocytes, it has been suggested that it might affect the vascular endothelium. Potassium has been used to induce endothelial denudation in vessels [3]. Other authors [4-6] have demonstrated that crystalloid cardioplegic solutions could alter the cellular morphology and the survival of cultured endothelial cells.

Previous studies have shown that 5-hydroxytryptamine (5-HT) causes an endothelium-dependent increase in coronary flow in the isolated perfused rat heart through the release of nitric oxide [7-9]. Nitric oxide is known as an endothelium-derived relaxing factor and thus may play a major role in vasoregulation and hemostasis. It inhibits platelet adhesion and aggregation and is also a powerful smooth muscle relaxant [10-13]. Besides endothelium-derived relaxing factor, the vascular endothelium produces prostacyclin, antithrombin III, and plasminogen activator, all of which prevent platelet aggregation and promote vasodilatation. Therefore, endothelial functional disturbances can cause flow impairment and might play a

role in the reperfusion syndrome after bypass operations [14-16].

Recently, it has been reported that crystalloid hyperkalemic cardioplegic perfusion could impair 5-HT endothelium-dependent coronary relaxation in the isolated Langendorff-perfused rat heart [17, 18]. Although potassium concentration was shown to be related to endothelial damage, these studies did not exclude other physical factors, such as CHCS infusion pressure and time exposure to CHCS. In the present study, the isolated, perfused rat heart model was used to investigate the effects of CHCS potassium concentration combined with infusion pressure and duration of CHCS exposure on endothelium-dependent coronary artery relaxation.

Material and Methods

Animal Preparation and Reagents

Hearts were obtained from male Sprague-Dawley rats (body weight, 250 to 300 g) maintained on a standard laboratory diet. 5-Hydroxytryptamine and sodium nitroprusside (SNP) were obtained from Sigma Chemicals Ltd, St. Louis, MO. Crystalloid hyperkalemic cardioplegia solution was made of standard lactated Ringer's solution to which KCl was added. All animals were cared for in compliance with the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH publication No. 85-23, revised 1985).

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Perfusion Technique

The rats were heparinized (3 mg/kg) and decapitated. The chest was immediately opened, and the aorta was isolated, cannulated, and perfused in vivo with 37°C oxygenated (95% O₂, 5% CO₂) Krebs-Ringer solution containing (in millimoles per liter): NaCl, 118.3; KCl, 4.7; MgSO₄, 1.2; KH₂PO₄, 1.22; CaCl₂, 1.3; NaHCO₃, 25.0; and glucose, 15; pH 7.4 at 37°C. The perfused hearts were excised from the chest and mounted onto a modified Langendorff apparatus [19]. Using this harvesting technique, myocardial ischemia was kept at less than 45 seconds. The perfusion pressure was maintained at 80 cm H₂O. The hearts were atrially paced at 300 to 350 beats per minute. The maximal left ventricular pressure and its first time derivative (dP/dt) were measured by inserting a latex balloon inside the left ventricle through the left atrium and inflating it to maintain a left ventricular end-diastolic pressure of 10 mm Hg. Left ventricular pressure was measured with a Gould transducer signal conditioner (Gould 20-4615-50, Cleveland, OH), and dP/dt was recorded using a Gould differentiator signal conditioner (Gould 13-G4615-71). The mean and pulsatile coronary flow were measured using a 2-mm factory-precalibrated cannulating ultrasonic probe (Transonic cannulating flow probe, type 2N; internal diameter, 3.2 mm; resolution, 0.1 mL/min; Transonic System Inc, Ithaca, NY) to which the aorta was attached. Two hearts were studied simultaneously in two Langendorff apparatuses and all data recorded in a eight-channel Gould recorder.

Drugs were dissolved in Krebs-Ringer solution and perfused with a Harvard syringe infusion pump 22 (Harvard Apparatus, South Natick, MA) to assure a constant drug delivery (5-HT, 1×10^{-6} mol/L; SNP, 1×10^{-5} mol/L) during coronary perfusion.

Protocol

After harvesting, hearts were perfused and stabilized for a period of 30 minutes in the Langendorff apparatus. At the end of this period, the coronary basal flow, left ventricular dP/dt, and left ventricular pressure were recorded for baseline values. Then 5-HT and SNP were sequentially infused into the rat aorta, through the cannula, for a period of 4 minutes each. Changes in coronary flow were recorded at the end of the 4-minute infusion. Each drug infusion was followed by a 30-minute washout period, to allow the coronary flow to return to control values. The drugs were always administered in the same sequence, 5-HT first followed by the SNP, 30 minutes later. After these steps, hearts were exposed to different cardioplegic solution perfusions as further described in the "Experimental Groups" section. This was followed by a 30-minute recovering period in which hearts were reperfused with 37°C Krebs-Ringer solution at 80 cm H₂O of perfusion pressure. Basal coronary flow, left ventricular dP/dt, and left ventricular pressure were recorded at the end of the recovering period. Hearts were then resubmitted to 5-HT and SNP infusion, and coronary flow changes were recorded as previously described.

Experimental Groups

In group I (n = 24), four subsets (n = 6) of isolated hearts were perfused with different potassium concentration solutions (12 mmol/L, 24 mmol/L, 40 mmol/L, and 100 mmol/L) at 80 cm H₂O of pressure and for a period of 30 minutes. In group II (n = 24), four subsets (n = 6) were exposed to the same potassium concentrations but the perfusion pressure was increased to 160 cm H₂O for a 30-minute exposure. In group III (n = 18), three subsets of hearts (n = 6) were exposed to CHCS containing 24 mmol/L, 40 mmol/L, and 100 mmol/L of KCl and the perfusion pressure was maintained at 160 cm H₂O but for a period of 10 minutes.

Data Analysis

Changes in coronary flow are reported as a percentage of the baseline value. Baseline flow is recorded in milliliters per minute. For statistical purposes, because the baseline flow was not necessarily the same throughout the experiment, differences in flow change before and after exposure to cardioplegia in the same group are reported as percent change and not mean change of the raw values. All data are expressed as the mean $\pm$ standard deviation. Statistical analysis was performed by Student's paired *t* test. The statistical significance of differences was established at 95% (*p* < 0.05).

Results

Group I (perfusion pressure, 80 cm H₂O; duration, 30 minutes)

Before CHCS perfusion both 5-HT and SNP caused a significant increase in coronary flow in all hearts. Coronary flow, with both drugs, did not change significantly after CHCS perfusion at all KCl concentrations, indicating that muscle tone and endothelial reactivity were still present (Fig 1).

Group II (perfusion pressure, 160 cm H₂O; duration, 30 minutes)

In this group, with the perfusion pressure doubled, the increase in coronary flow caused by SNP remained unaffected at all potassium concentrations. However, the 5-HT vasodilatory effect was severely decreased (*p* < 0.01) at KCl concentrations of 24 mmol/L or more (Fig 2). At a KCl concentration of 100 mmol/L, the endothelial response was virtually abolished (mean flow increase before infusion, 40% $\pm$ 10%; after infusion, 2% $\pm$ 18%; *p* < 0.01).

Group III (perfusion pressure, 160 cm H₂O; duration, 10 minutes)

When the same high perfusion pressure was used but the duration of perfusion was decreased to 10 minutes, the increase in coronary flow induced by 5-HT and SNP infusion did not change significantly by CHCS infusion at any potassium concentrations (Fig 3).

Ventricular Function

Left ventricular pressure and dP/dt remained unchanged after CHCS infusion in all these experiments, indicating

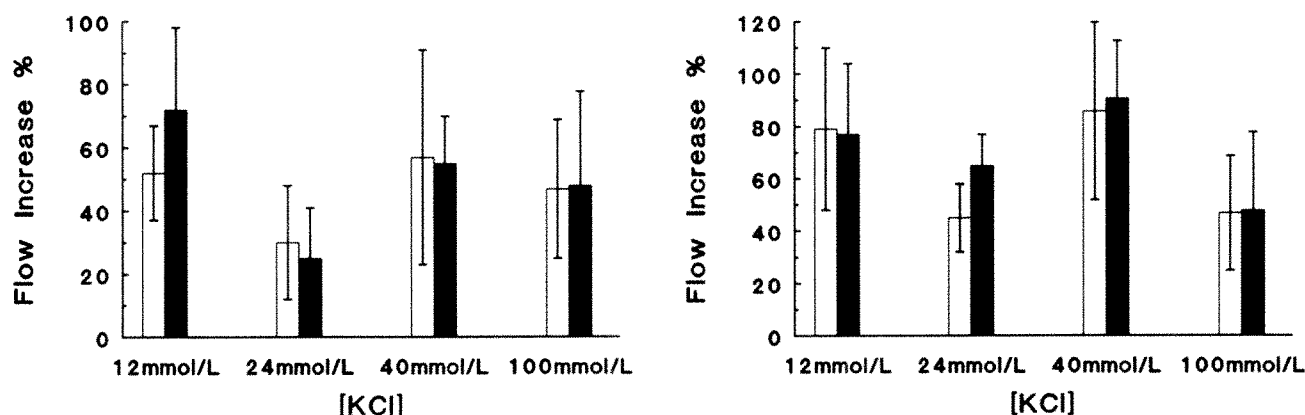


Fig 1. Percentage increase in coronary flow induced by (A) 5-hydroxytryptamine (10^{-6} mmol/L) and (B) sodium nitroprusside (10^{-5} mmol/L) before (open bars) and after (solid bars) a 30-minute infusion at a pressure of 80 cm H₂O of hyperkalemic cardioplegic solutions containing 12, 24, 40, and 100 mmol/L of KCl.

that the hearts were functionally unaffected throughout the study (Table 1).

Baseline Flow

Baseline coronary flow decreased significantly after CHCS exposure in all groups (Table 2). One group failed to record a significant decrease in baseline flow (first subset of group III: 160 cm H₂O of perfusion pressure, 10-minute perfusion time, 24 mmol KCl/L), and this could be related to a larger variability in this group (9.3 ± 0.9 mL/min versus 8.15 ± 2.7 mL/min; p = not significant).

Comment

Nitric oxide release is one of the major functional aspects of the vascular endothelium. Nitric oxide inhibits platelet adhesion and aggregation, and is also a powerful vasodilator [10-13]. Serotonin has been shown to promote nitric

oxide release in rat coronaries [7, 8]. In the present study, the combined effect of KCl concentration, perfusion pressure, and duration of exposure was analyzed. The results indicate that in the rat, a perfusion of 30 minutes with crystalloid cardioplegic solution containing up to 100 mmol/L of KCl had no effect on 5-HT endothelium-dependent coronary vasodilatation when a perfusion pressure of 80 cm H₂O was used. Increasing the perfusion pressure to 160 cm H₂O severely decreased the coronary endothelial vasodilator response to 5-HT in hearts exposed to CHCS containing 24 mmol/L or more of KCl. Decreasing the duration of exposure to CHCS neutralized the detrimental effect of high infusion pressure and provided protection of the endothelial function even at very high potassium concentrations (100 mmol/L). Sodium nitroprusside-induced coronary vasodilatation remained unaffected at all KCl concentrations, perfusion pressures, and duration of exposures studied, indicating that the

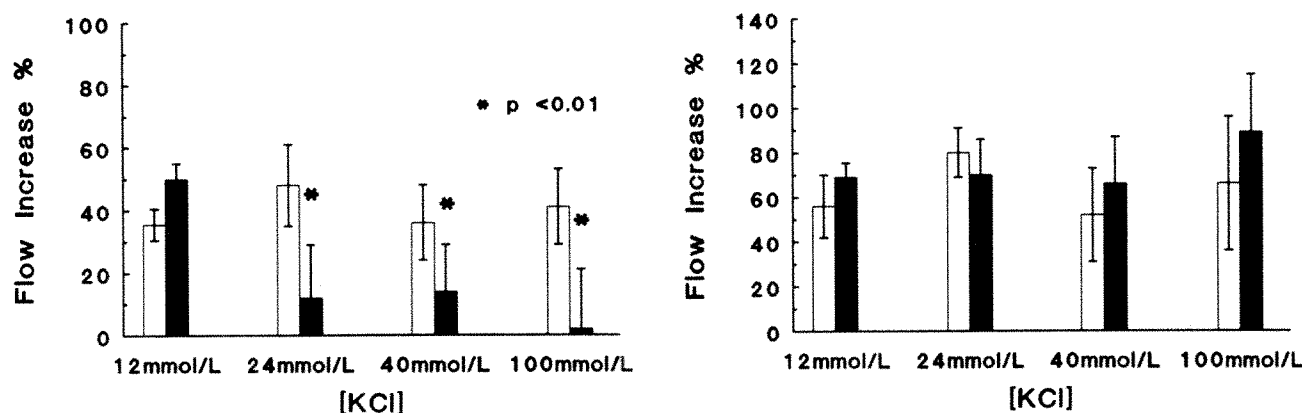


Fig 2. Percentage increase in coronary flow induced by (A) 5-hydroxytryptamine (10^{-6} mmol/L) and (B) sodium nitroprusside (10^{-5} mmol/L) before (open bars) and after (solid bars) a 30-minute infusion at a pressure of 160 cm H₂O of hyperkalemic cardioplegic solutions containing 12, 24, 40, and 100 mmol/L of KCl. The difference in response to 5-hydroxytryptamine is significant ($p < 0.01$), whereas the response to sodium nitroprusside remained similar.

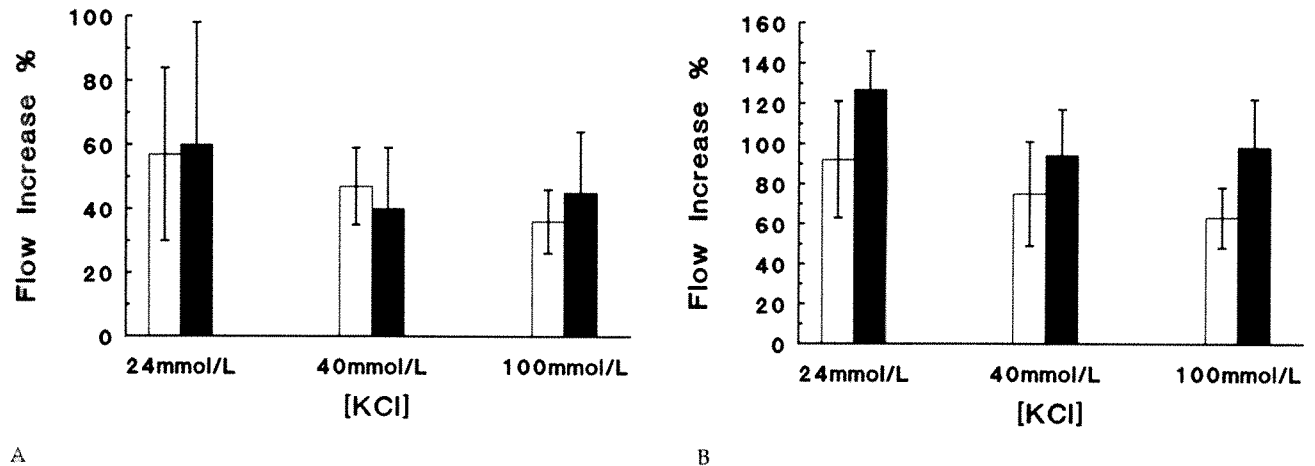


Fig 3. Percentage increase in coronary flow induced by (A) 5-hydroxytryptamine (10^{-6} mmol/L) and (B) sodium nitroprusside (10^{-5} mmol/L) before (open bars) and after (solid bars) a 10-minute infusion at a pressure of 160 cm H₂O of hyperkalemic cardioplegic solutions containing 24, 40, and 100 mmol/L of KCl.

smooth muscle reactivity was not altered by the various perfusion conditions. Similarly, left ventricular pressure and dP/dt were not significantly affected, suggesting little ischemic damage to the myocardium during the experiments. Therefore, it is conceivable that the endothelium was protected from ischemic damage. However, basal flow was constantly diminished after CHCS infusion. Perfusion pressures of 80 and 160 cm H₂O were selected

because they explore the whole spectrum of the normal blood pressure in the rat (diastole, 60 to 90 mm Hg; systole, 110 to 130 mm Hg) [20] and they represent the perfusion pressure that rat coronary arteries are normally exposed to.

Evidence of CHCS-induced endothelial injury has been previously reported. In regard to endothelial cell survival, Carpentier and co-workers [4] studied the cytotoxicity of 12 different cardioplegic solutions using the tissue culture technique. A cell death rate of 4.2% to 13.1% was found after 3 hours of incubation (10°C) with all cardioplegic solutions. However, the role of hyperkalemia per se was not specifically evaluated. Von Oppel and associates [21], using the same model, performed a similar study on

Table 1. Left Ventricular dP/dt and Maximal Left Ventricular Pressure Before and After Crystalloid Hyperkalemic Cardioplegia Infusion Without 5-Hydroxytryptamine or Sodium Nitroprusside Stimulation^a

Group	dP/dt (mm Hg/s)		LVP (mm Hg)	
	Before	After	Before	After
Group I (KCl, mmol/L)				
12	1,400 ± 330	1,200 ± 360	58 ± 6	51 ± 11
24	2,965 ± 795	1,890 ± 840	92 ± 24	62 ± 20
40	2,170 ± 930	1,890 ± 400	95 ± 16	90 ± 26
100	1,830 ± 380	1,290 ± 285	73 ± 29	53 ± 22
Group II (KCl, mmol/L)				
12	2,050 ± 280	1,500 ± 550	71 ± 10	57 ± 11
24	2,100 ± 480	1,700 ± 500	76 ± 15	60 ± 10
40	1,900 ± 580	1,700 ± 500	83 ± 15	68 ± 17
100	1,250 ± 200	1,050 ± 190	67 ± 4	50 ± 8
Group III (KCl, mmol/L)				
24	1,680 ± 350	1,320 ± 300	74 ± 10	62 ± 8
40	1,850 ± 350	1,650 ± 300	77 ± 12	65 ± 11
100	1,130 ± 220	1,030 ± 220	63 ± 6	58 ± 5

^a No significant change before and after crystalloid hyperkalemic cardioplegia.

dP/dt = first time derivative of left ventricular pressure; LVP = maximal left ventricular pressure.

Table 2. Coronary Baseline Flow Before and After Infusion of Cardioplegic Solutions

Group	Baseline flow (mL/min)		<i>p</i> Value
	Before	After	
Group I (KCl, mmol/L)			
12	10.5 ± 1.6	8.6 ± 1.2	<0.01
24	10.1 ± 2.4	7.4 ± 2.0	<0.01
40	11.7 ± 2.2	8.9 ± 2.3	<0.01
100	9.7 ± 1.5	6.7 ± 1.3	<0.01
Group II (KCl, mmol/L)			
12	9.2 ± 0.5	7.3 ± 0.7	<0.01
24	11.8 ± 1.5	10.0 ± 1.9	<0.05
40	11.4 ± 1.9	8.4 ± 1.6	<0.05
100	9.9 ± 1.6	7.6 ± 0.9	<0.05
Group III (KCl, mmol/L)			
24	9.3 ± 0.9	8.2 ± 2.7	NS
40	11.1 ± 1.2	8.6 ± 1.3	<0.05
100	9.5 ± 0.8	7.5 ± 1.0	<0.01

NS = not significant.

solid-organ preservation solutions and endothelial cell toxicity. Different intracellular and extracellular types of preservation solutions were studied and no detrimental effect on cell survival related to high potassium concentrations (up to 115 mmol/L), as in the Collins solution, could be demonstrated. As for structural defects, Solberg and colleagues [5, 22] described morphological damage at scanning and transmission electron microscopy when cultured endothelial cells were incubated with either the St. Thomas or the Bretschneider solution (containing, respectively, 20 and 10 mmol/L of KCl), but these changes were only transient and reversed almost completely after rewarming in the culture medium for 35 minutes. Follette and associates [6] and Harjula and colleagues [23] have shown a loss of endothelium and an increase in platelet deposition in coronary arteries submitted to hyperkalemic (20 mmol/L of KCl; perfusion pressure, 80 mm Hg) crystalloid cardioplegic solution.

Besides causing morphological changes to the endothelium, CHCS can also damage endothelial secretory function. Saldanha and Hearse [17] and Mankad and associates [18] reported deleterious effects of hyperkalemic CHCS on 5-HT-induced endothelium-dependent coronary vasodilatation. Their study showed a severe decrease in endothelium-dependent vasodilatation after exposure to St. Thomas or Bretschneider solutions containing 25 mmol/L or more of KCl. In both experiments, CHCS perfusion pressure was maintained at 100 cm H₂O for a period of 30 minutes or more. Compared with our results, more endothelial damage was obtained by these authors at lower KCl concentrations. This may be due to the higher perfusion pressure (100 instead of 80 cm H₂O) and to the different cardioplegic solutions used in their experiments. The effect of MgCl (present at a concentration of 16 mmol/L in the St. Thomas solution) on the vascular endothelium is not known. Bretschneider solution contains 7.3 mmol/L of procaine hydrochloride, which has been reported to increase cytotoxicity of CHCS on cultured endothelial cells [5]; it could therefore potentially affect endothelium-derived relaxing factor release by the endothelium.

The purpose of the present study was to examine the effect of different KCl concentrations combined with mechanical and time factors on endothelial function. Lactated Ringer's solution, with KCl the only added component, was chosen to minimize chemical interactions. One possible flaw of our study is that the osmolarity was not corrected when a high KCl concentration was added. However, significant damage was obtained with CHCS containing 24 mmol/L of KCl, whereas the osmolarity of the solution is 313 osm/L, which is still in a normal range. Therefore, high osmolarity cannot be the only responsible factor for endothelial dysfunction.

Basal coronary flow was constantly decreased after CHCS perfusion, suggesting a decrease in the basal endothelium-derived relaxing factor release by the resting endothelium. However, other contributing factors such as a decrease in prostacyclin production or myocardial swelling and stiffness as the experience goes on could contribute to this drop in basal coronary flow [24]. Any endothe-

lial alteration may be the cause of platelet aggregation and vasospasm due to the release of vasoactive compounds, causing the unprotected smooth muscle to contract and as a result contribute to poor myocardial performance in clinical situations [15].

Because the 5-HT-induced coronary relaxation was preserved, it can be inferred that the coronary vessels were still protected against platelet aggregation and thrombus formation by normal release of endothelium-derived relaxing factor.

Our results indicate that it is possible to perfuse high potassium concentrations with minimal endothelial dysfunction, provided that pressure and duration of exposure are also considered. A high KCl concentration appears to be well tolerated at a low perfusion pressure and for a short period of exposure. This indicates that KCl concentration is not the only damaging factor and other physical factors must also be considered to avoid functional damage to the endothelium during CHCS perfusion. This finding may be of clinical significance in myocardial protection during cardiac operations.

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Paranasal Sinusitis: Cryptic Sepsis After Coronary Artery Bypass Operations

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Infections occurred in 52 of 400 patients (13%) undergoing coronary artery bypass operations from January 1987 to December 1990. The hospital courses of 5 patients (1.3%) in whom occult infections of the paranasal sinuses developed were reviewed. Only 1 patient had specific clinical findings of acute sinusitis (purulent nasal discharge). Computed tomography showed wall thickening, opacification, or air-fluid levels in one or more paranasal sinuses in each patient. All patients were successfully treated with surgical drainage and antibiotics. Risk fac-

tors for development of postoperative acute sinusitis include: prolonged tracheal intubation, airway colonization with nosocomial bacteria, inability to clear nasal secretions, sinus ostial obstruction, and critical organ system dysfunction. Physical examination and roentgenographic evaluation of the paranasal sinuses should be considered when postoperative sepsis of obscure etiology occurs.

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Infections are a source of major morbidity and mortality after cardiac operations. Sepsis may be the result of pneumonia, mediastinitis, urinary tract infections, endocarditis, or infected prosthetic materials [1, 2]. When inadequately treated, sepsis results in multisystem organ failure and death.

In 1985 one of us (C.E.B.) performed a coronary artery bypass operation (CAB) on a patient in whom postoperative sepsis and multisystem organ failure developed. An exhaustive search for a septic source was unsuccessful. The patient died despite administration of broad-spectrum antibiotics and intensive supportive care. Autopsy revealed suppurative maxillary sinusitis as the probable site of sepsis. We present 5 similar patients and discuss their clinical course and management.

Material and Methods

Methods

We retrospectively reviewed the records of 400 consecutive patients undergoing CAB from January 1987 to December 1990. In 52 patients (13%) postoperative infections developed based on clinical and laboratory data or on pathologic tissue examination. These cases included wound infection (20), pneumonia (19), urinary tract infection (6), postoperative acute sinusitis (PAS) (5), mediastinitis (4), catheter sepsis (2), occult bacteremia (2), molar abscess (1), and acalculous cholecystitis (1).

The 5 patients in whom PAS developed (4 male, 1 female) were 53 to 73 years old (mean 63.4 years). The

diagnosis in all patients was based on (1) an abnormal computed tomographic scan of the paranasal sinuses defined as wall thickening, cavity opacification, or presence of air-fluid levels and (2) the finding of pus at the time of sinus aspiration or surgical drainage.

All patients undergoing CAB routinely received perioperative antibiotic prophylaxis consisting of 1 g of cefadyl intravenously at the time of induction and then every 6 hours for 48 hours. All patients had primary intraoperative orotracheal intubation. After routine extubation, 17 patients required reintubation (14 oral and 3 nasal). None of the patients in whom PAS developed were nasally intubated. One patient (patient 1) had an unsuccessful attempt at nasotracheal intubation. The 5 patients with PAS were endotracheally intubated from 10 to 27 days (mean, 14.2 days) before a diagnosis of PAS (Table 1). The 395 CAB patients without PAS were intubated from 1 to 23 days (mean, 1.4 days).

Nasal or oral gastric sump tubes for decompression (16F or 18F) were routinely placed intraoperatively and removed after tracheal extubation. Patients with PAS had nasogastric drainage tubes in place from 1 to 12 days (mean, 8.6 days) before a diagnosis of PAS, whereas the 395 CAB patients without PAS had nasogastric drainage for 0 to 23 days (mean, 1.3 days). The side of the nasal intubation could only partially be determined from review of the patient records.

Culture-specific systemic antibiotics were administered in 4 patients with PAS (Table 2). Three patients (patients 1, 2, and 5) were already receiving broad-spectrum antibiotics to which the putative organism(s) were sensitive. In 1 patient (patient 4) empiric vancomycin administration had been discontinued 48 hours before sinus drainage but the course was resumed upon obtaining productive bacterial cultures from the sinus drainage. One patient (pa-

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Opinions expressed herein are those of the authors and not necessarily those of the Air Force or the Department of Defense.

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Table 1. Endotracheal and Gastric Tubes in Patients With Postoperative Acute Sinusitis

Patient No.	Endotracheal Intubation (days)	Gastric Intubation (days)
1	13 (O) ^{a,b}	11 GT (N) (8 via right nares)
2	10 (O)	10 GT (N)
3	11 (O)	9 GT (N) (7 via left nares) 1 GT (O) 1 FT (N)
4	10 (O)	1 GT (N) (1 via left nares) 3 GT (O) 5 FT (N) (5 via left nares)
5	27 (O)	12 GT (N) 15 FT (N)

^a Successive intubations of 1, 2, and 10 days' duration. ^b Attempted nasal tracheal intubation at second reintubation.

FT = small-diameter feeding tube; GT = 16F to 18F gastric sump drainage tube; N = nasal; O = oral.

tient 3) in whom a definitive organism was not identified was treated with empiric clindamycin and ceftazidime.

One patient (patient 5) was treated unsuccessfully with topical phenylephrine hydrochloride (Neo-Synephrine; Winthrop Pharmaceuticals, New York, NY) and antibiotics for several days before surgical drainage. Aspiration and irrigation of an infected maxillary sinus was unsuccessful in eradicating a multiple sinus cavity infection in 1 patient (patient 1). Surgical pansinus endoscopic exploration and drainage of the infected sinuses was ultimately performed in all patients. Nasogastric drainage and feeding tubes were removed before exploration.

Each patient with PAS had preexisting organ system dysfunction (Table 3). All patients had pulmonary failure necessitating prolonged endotracheal intubation, 4 had renal failure (3 requiring dialysis), 3 had cardiac dysfunction (1 required a left ventricular assist device and an intraaortic balloon pump, 1 required an intraaortic balloon pump only, 1 required mediastinal reexploration for tam-

ponade) and 2 patients had central nervous system dysfunction (1 remaining comatose until death). Four patients had evidence of sepsis from sources in addition to the paranasal sinuses (respiratory tract, 4; tooth abscess, 1).

Case Presentations

PATIENT 1. Patient 1 is a 69-year-old man who underwent an urgent triple CAB. On postoperative day (POD) 3 a left *Enterobacter aerogenes* pneumonia developed. Multiple cultures of blood, sputum, urine, and intravascular catheters were negative. Due to persistent fever and leukocytosis on POD 9 the mediastinum was explored and found to be negative on Gram stain and bacterial culture. A subsequent sinus roentgenographic series was normal. The patient's mental acuity decreased but computed tomography of the brain and cerebrospinal fluid analysis were normal. The head computed tomogram did show opacification of the right maxillary sinus, and on POD 16, 1.5 mL of pus was aspirated from the sinus. Gram-negative rods and leukocytes were identified on fluid Gram stain. Cultures of the fluid grew *Proteus mirabilis*. Within 24 hours the patient's temperature decreased and the leukocyte (WBC) count returned to normal. Two days later the patient's fever recurred and the WBC count rose to $19.2 \times 10^9/L$ ($19,200/\mu L$). The left sphenoid sinus was surgically drained and the temperature and the WBC count rapidly normalized. The patient's respiratory and renal failure slowly improved.

PATIENT 2. Patient 2 is a 59-year-old man who underwent urgent sextuple CAB. A perioperative coagulopathy and cardiac tamponade developed, requiring three mediastinal explorations during the first 36 hours after CAB. On POD 2 adult respiratory distress syndrome and subsequent renal dysfunction developed. Multiple cultures of blood, sputum, urine, and intravascular catheters were negative. Sputum Gram stain showed WBCs with gram-positive cocci; a single sputum specimen grew *Candida albicans*. Computed tomography of the brain was normal but showed opacification of the ethmoid and sphenoid

Table 2. Summary of Bacteriologic and Antibiotic Data in Patients With Postoperative Acute Sinusitis (PAS)

Patient No.	Organism ^a	Colonization of Tracheobronchial Tree	Blood Culture	Antibiotic Regimen
1	<i>Proteus mirabilis</i>	<i>Proteus mirabilis</i> , <i>Xanthomonas maltophilia</i> , <i>Enterobacter aerogenes</i>	Negative	Imipenem, amikacin
2	<i>Staphylococcus epidermidis</i>	Gram-positive cocci, <i>Candida albicans</i>	Negative	Imipenem, gentamicin ^b , cephapirin ^b
3	None isolated	<i>Escherichia coli</i> , <i>Candida albicans</i>	Negative	Clindamycin, ceftazidime
4	<i>Staphylococcus epidermidis</i>	<i>Staphylococcus aureus</i> , <i>Enterobacter cloacae</i> , <i>Acinetobacter calcoaceticus</i> , <i>Candida albicans</i>	Negative	Gentamicin, clindamycin, vancomycin ^b
5	<i>Staphylococcus epidermidis</i>	<i>Staphylococcus epidermidis</i> ^c , <i>Streptococcus</i> , <i>Xanthomonas maltophilia</i>	<i>Staphylococcus epidermidis</i>	Imipenem, gentamicin, vancomycin, trimethoprim-sulfamethoxazole

^a Putative pathogenic organism responsible for sinus infection. only once 3 weeks before sinus infection.

^b Discontinued 48 hours before sinus drainage procedure.

^c Cultured from sputum

Table 3. System Dysfunction and Sepsis Before Postoperative Acute Sinusitis

Patient No.	Sepsis (source)	Respiratory Failure (cause)	Cardiac Dysfunction (cause)	Renal Insufficiency	Central Neurologic Event	Length of Unresponsive State ^a (days)
1	Yes (pulmonary)	Yes (pneumonia)	No	Yes (dialysis)	No	5
2	No	Yes (ARDS, pulmonary edema)	Yes (tamponade) ^b	Yes ^c	No	10
3	Yes (pulmonary, tooth abscess)	Yes (ARDS, pulmonary edema, pneumonia)	Yes (primary myocardial dysfunction) ^b	Yes (dialysis)	Yes (transient seizures)	6
4	Yes (pulmonary)	Yes (ARDS, pneumonia)	Yes (primary myocardial dysfunction) ^b	Yes (dialysis)	Yes (coma)	10
5	Yes (pulmonary)	Yes (ARDS, pneumonia)	No	No	No	27

^a Represents length of time unresponsive secondary to unconsciousness, sedation, or muscle relaxation before development of sinusitis. ^b See text for details. ^c Nonoliguric azotemia and increase in serum creatinine level.

ARDS = adult respiratory distress syndrome.

sinuses (Fig 1). The sinuses were surgically drained on POD 10. Cultures of fluid from the right ethmoid and left sphenoid sinuses grew *Staphylococcus epidermidis*. Within 48 hours the patient's temperature dropped to 38.3°C and the WBC count declined to $13.9 \times 10^9/L$ ($13,900/\mu L$). The patient's multisystem organ failure slowly resolved.

PATIENT 3. Patient 3 is a 53-year-old man who underwent emergent quadruple CAB. An intraaortic balloon pump and a left ventricular assist device were required to separate the patient from cardiopulmonary bypass. Adult respiratory distress syndrome developed, with subsequent *Escherichia coli* pneumonia and seizures. An abscessed lower molar tooth (*Staphylococcus coagulase negative*) was removed on POD 2, and by POD 3 all mechanical assist devices were removed. He demonstrated a septic course associated with progressive renal dysfunction. Due to purulent nasopharyngeal drainage a head computed tomogram was obtained, which showed a right maxillary sinus air-fluid level (Fig 2). On POD 11 he underwent surgical drainage and removal of purulent material from the right maxillary and sphenoid sinuses. Although no bacteria were isolated, the patient had immediate improvement of his clinical course.

PATIENT 4. Patient 4 is a 73-year-old man who underwent elective quintuple CAB. He suffered an intraoperative ventricular fibrillatory arrest and required both inotropic support and an intraaortic balloon pump. Consolidation of the left lower lung and adult respiratory distress syndrome developed. Multiple gram-negative bacteria and *Staphylococcus epidermidis* were cultured from the sputum. Renal dysfunction necessitated hemodialysis. A head computed tomogram to evaluate progressive alteration in mental status showed an air fluid level in the right maxillary sinus, which was then surgically drained on POD 10. *Staphylococcus epidermidis* was isolated from the sinus. After a brief period of improvement the patient again became septic. Acute acalculous cholecystitis was identified and surgically treated, but the patient eventually died of multisystem organ failure on POD 37.

PATIENT 5. Patient 5 is a 63-year-old woman with chronic obstructive pulmonary disease who underwent emer-

gency quadruple CAB. Pneumonia (probably gram positive) and adult respiratory distress syndrome developed on POD 3. Direct fiberoptic nasal examination revealed fluid in the maxillary sinuses. Treatment was begun with topical (Neo-Synephrine) and systemic antibiotics. She transiently improved, but then fever, leukocytosis, and culture-proven *Staphylococcus epidermidis* bacteremia developed. Head computed tomography showed opacification of all paranasal sinuses. All sinuses were surgically drained. Pus drained from the right maxillary sinus grew *Staphylococcus epidermidis*. Within 24 hours the patient's temperature and WBC count normalized. The patient's sepsis and multisystem organ failure resolved but she remained ventilator dependent. She died 4 months postoperatively after voluntary cessation of mechanical ventilation.

Results

Purulent nasopharyngeal drainage was observed in only 1 patient with PAS (patient 3). Patients with PAS were



Fig 1. (Patient 2.) Computed tomographic scan demonstrating partial opacification of the ethmoid sinus, greater on the right (arrow), and bilateral opacification of the sphenoid sinuses (arrowheads).

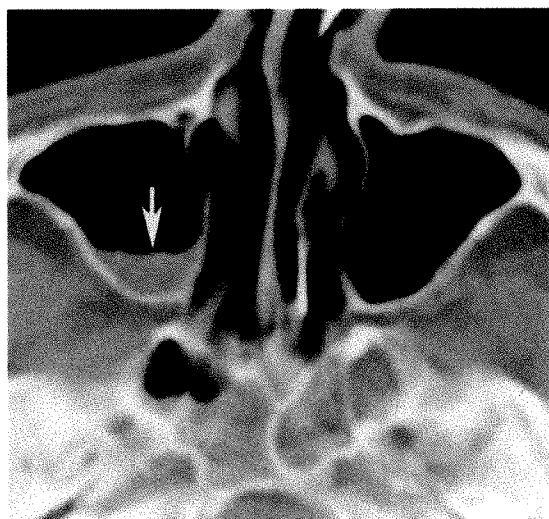


Fig 2. (Patient 3.) Computed tomographic scan demonstrating a right maxillary sinus air-fluid level (arrow).

febrile (38.7° to 39.8°C) and had leukocytosis (16 to 26.7 $\times 10^9/L$ [16,000/ μL to 26,700/ μL]). Other indicators of sepsis including tachycardia (120 to 125 beats/min), an inappropriately high cardiac index (3.0 to 4.4 $L \cdot min^{-1} \cdot m^{-2}$), systolic arterial hypotension (60 to 90 mm Hg), low systemic vascular resistance (600 to 740 dyne-s/cm⁵) and an increased catabolic rate (urinary urea nitrogen excretion of 26.4 to 30.3 g/24 h) were documented in 4 patients (Table 4).

Infected sinuses in patients with PAS included maxillary (4), sphenoid (3), and ethmoid (1); 3 patients (60%) had more than one infected paranasal sinus. Single organisms were cultured from the sinus drainage in 4 of the 5 patients with PAS (see Table 2). The tracheobronchial tree in all 5 patients was colonized by multiple organisms. In 1 patient (patient 1) *Proteus mirabilis* was cultured simultaneously from both the sinus and tracheobronchial tree. One patient (patient 5) had a documented bacteremia with the same organism isolated from the sinus drainage.

Two deaths occurred in the PAS group. One resulted from multisystem failure secondary to acalculous cholecystitis; the other occurred from respiratory failure after the patient and her family requested removal of long-term mechanical ventilation.

Comment

Acute sinusitis is reportedly responsible for 5% of all infection in trauma units and occurs in up to 25% of patients with central nervous system injury [3, 4]. Patients undergoing CAB previously have not been reported to be at serious risk for postoperative sinusitis. Cryptic sinus infections occurred in 1.3% of our CAB patients, which represents 9.6% of all of our postbypass infections. Postoperative acute sinusitis occurred only in patients who had a prolonged and complicated postoperative intensive care unit course.

Factors associated with occurrence of sinusitis in patients in the intensive care unit include maxillofacial

trauma, sedation, corticosteroids, and nasogastric catheterization [5-7]. However, nasotracheal intubation, especially if emergent or traumatic, is implicated as the leading cause of PAS [4, 8-12]. Bacteremia during nasal tracheal intubation and the direct obstruction of the paranasal sinus ostia by the characteristically large and stiff tube are thought by some to be etiologic [13]. Nasotracheal intubation was rarely performed in our patients. One patient underwent an attempted nasotracheal intubation, which resulted in a mucosal injury and possible sinus ostial occlusion.

Nasogastric tubes are also implicated in the development of PAS by causing mucosal irritation with subsequent sinus ostial obstruction [6, 8]. In our series, although nasogastric tubes remained in place on the average longer in patients with PAS than in those without PAS, in 3 patients infections occurred in sinus cavities contralateral to the nasogastric tube. This observation suggests that factors other than local obstruction may also be important.

Each patient had respiratory failure requiring prolonged oral tracheal intubation, and all patients had culture-documented colonization of the tracheobronchial tree. Although only 1 patient had an identical organism cultured simultaneously from tracheobronchial and sinus aspirates, the profile of bacteria cultured from the infected sinus could be anticipated as a result of usual nosocomial colonization. Broad-spectrum empiric antibiotics may have been incompletely effective and contributory to infection by selecting out resistant organisms. We would agree with others that opportunistic organisms responsible for PAS are dissimilar from the predominant *Streptococcus* and *Haemophilus* species occurring in outpatient sinusitis and that factors promoting colonization of the paranasal sinuses are important in the development of this disease [5-8, 11].

All patients with PAS had a prolonged period of immobility because of unconsciousness or administration of muscle relaxants to assist in mechanical ventilation. Our patients were similar in this way to those reported with central neurologic emergencies or trauma in whom PAS subsequently developed [5]. The inability of these patients to normally clear secretions may have promoted paranasal sinus colonization and ostial obstruction.

Table 4. Results in Patients With Postoperative Acute Sinusitis

Patient No.	Paranasal Sinus Cavities Infected	Complications	Outcome
1	Right maxillary, left sphenoid	Sepsis ^a	Alive
2	Right ethmoid, left sphenoid	Sepsis ^a	Alive
3	Right maxillary, right sphenoid	Sepsis ^a	Alive
4	Right maxillary	...	Dead ^b
5	Right maxillary	Sepsis ^a , bacteremia	Dead ^c

^a See text for details. ^b Autopsy-proven acalculous cholecystitis and bile peritonitis. ^c Patient request for discontinuance of ventilatory support.

Critical illness and organ system dysfunction reflected as a mean APACHE II score of 20.36 has been correlated with development of PAS in trauma patients [6]. Although APACHE II scoring cannot be applied to patients after cardiac operations [14], our patients with PAS had serious perioperative complications resulting in major organ system dysfunction. Frequent nonsinus postoperative sepsis likely contributed to this process.

Diagnosis of acute sinusitis in unconscious critically ill patients is difficult because of the paucity of physical signs and symptoms [6, 8, 11]. Typically, the patient with PAS has sepsis of "cryptic" etiology as was seen in our series. Nonspecific signs such as fever and leukocytosis are often present; however, characteristic findings of PAS such as nasopharyngeal purulence are rare.

Previous reports suggest plain sinus roentgenograms, including a Water's view, are 90% accurate in diagnosing PAS. Sinus series radiographs obtained in 1 patient (patient 1) were not helpful. We found computed tomographic findings of PAS to be uniformly diagnostic. Moreover, involvement of the sphenoid or ethmoid sinuses (3 patients) is identified best by computed tomographic radiography [8, 11, 15, 16]. Hansen and associates [10] prospectively evaluated computed tomography of the paranasal sinuses in a group of 12 patients with central nervous system pathology who had undergone nasotracheal intubation. They found that 100% of the patients had radiographic evidence of PAS less than 3 days after intubation, and positive cultures from nasal purulent discharge eventually developed in 7 patients.

Several authors report good results with nonoperative measures including removal of nasal tubes, antibiotics, and topical decongestants [5, 7, 8, 10, 12, 17]. Twenty percent to 50% of patients in these reported series ultimately required therapeutic sinus aspiration and irrigations. In our series, treatment of PAS consisted of removal of all nasal tubes, administration of antibiotics, and surgical drainage. We are impressed with the rapid clinical improvement after surgical drainage.

Eighteen percent to 83% of patients with PAS are reported as having bacteremias [4, 6, 7, 17]. Only 1 patient in our series had a bacteremia. None of our patients had development of meningitis or brain abscess, which are reported sequelae of PAS [5, 7]. No deaths in our series were related to PAS. Again, our aggressive management of PAS may have minimized the morbidity.

We agree with reports that prevention of PAS centers around refraining from the use of large-diameter nasal tracheal tubes, which has been our practice. All nasogastric tubes (including feeding tubes) should be removed as early as possible or placed transorally. Frequent suctioning of nasopharyngeal secretions should help clear nasal airways and facilitate sinus drainage. We cannot substantiate whether prophylactic antibiotic therapy or topical decongestants will afford prophylaxis against occurrence of PAS. Routine preoperative nasal cultures are unlikely to forecast the profile of postoperative colonization of the nasopharynx. Such cultures would not aid in determining an appropriate antibiotic regimen.

Postoperative acute sinusitis is an uncommon complication after CAB operations. The infection typically occurs in patients with a protracted and complicated postoperative course. Patients requiring prolonged oral or nasal endotracheal intubation will have nosocomial colonization of the nasopharyngeal and tracheobronchial airways and will be at risk for PAS. Inability to clear nasal secretions may also predispose to development of PAS. Critically ill and physiologically stressed patients immunocompromised by augmented postoperative stress responses may be at particular risk. A high index of suspicion and well-planned radiographic diagnostic interventions are necessary to make the diagnosis of occult PAS. Surgical drainage is followed by immediate improvement and should be considered the treatment of choice.

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Influence of Temperature of Flushing Solution on Lung Preservation

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For lung transplantation the technique of flushing the donor pulmonary vascular bed may provide advantages in lung preservation such as rapid cooling and washout of blood. However, rapid cooling of the ischemic lung may also produce adverse effects. The aim of this study was to compare methods of cold flushing and topical cooling, and to evaluate the effect of temperature of the flushing solution on lung preservation. A total of 25 rabbit lungs were studied. Using an ex vivo rabbit lung model, postischemic function was assessed by the ability of the lung to oxygenate perfused blood and by measurement of pulmonary artery and airway pressures. The lungs in group I were preserved with simple immersion at 10°C for 30 hours. The lungs in groups II through V were flushed with solution containing phosphate-

buffered dextran (LPD) at different temperatures (groups II and IV, 10°C; groups III and V, 23°C) and stored at 10°C for various ischemic periods (groups II and III, 30 hours; groups IV and V, 36 hours). Pulmonary vascular resistance during flushing at 10°C was significantly higher than that at 23°C ($p < 0.001$). Flushing resulted in better preservation than topical hypothermia. Flushing at 23°C resulted in superior postischemic function compared with flushing at 10°C. We conclude that in lung preservation, uniform flushing with LPD solution improves the ischemic tolerance as compared with topical hypothermia, and that flushing with solutions at too low temperatures may have adverse effects on lung preservation.

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Flushing of the pulmonary vascular beds has been used in both experimental and clinical studies of lung preservation [1, 2]. Compared with preservation of the kidneys and liver, however, the results with flush preservation of the lung have been much less satisfactory.

Haverich and associates [2] reviewed the history of lung preservation and pointed out that many factors contributing to flush preservation have not yet been defined. One of these is the temperature of the flushing solution, which may be different from the optimum storage temperature.

Basically, the flushing technique in organ preservation can provide some advantages but may also be harmful. Flushing of the graft organs with solutions at low temperature may facilitate the rate of cooling but may also cause vasoconstriction with resulting incomplete perfusion of some areas of the lung, as well as cellular edema [3].

In this study, an ex vivo perfused rabbit model was used to compare the effects of cold flushing with topical cooling, and also to evaluate the influence of temperature of the flushing solution on lung preservation.

Material and Methods

Five groups ($n = 5$ for each group) of 3.2- to 3.5-kg white New Zealand rabbits' lungs were studied ex vivo using an

isolated perfused lung preparation, which was simplified from the previously described model [4]. The techniques of pulmonary artery cannulation and heart-lung block harvesting were similar to the previous model [4].

The rabbits were premedicated with subcutaneous atropine sulfate (0.25 mg/kg), ketamine (35 mg/kg), and acepromazine maleate (0.6 mg/kg). They were then anesthetized with intravenous sodium pentothal (25 mg/kg), and heparin (700 IU/kg) was administered into the ear vein. A cervical tracheostomy was rapidly performed and the trachea was intubated with a No. 3 endotracheal tube, which was then connected to a volume-cycled respirator (Harvard model 671). The lungs were ventilated with room air at a respiratory rate of 45 per minute, a tidal volume of 25 mL, and 0.5 cm H₂O of positive end-expiratory pressure.

The chest was opened by median sternotomy, and the superior vena cavae, ascending aorta, and pulmonary artery were mobilized and loosely encircled with ligatures. The pulmonary artery was cannulated with a 14F catheter through the right ventricular outflow tract for subsequent flushing of the lungs. This cannula was also used to measure mean pulmonary artery pressure (PAP). A drainage tube was placed into the left ventricle, and the animal was exsanguinated, which required less than 20 seconds. The pulmonary artery ligature was tied to secure the pulmonary artery cannula in place and the ascending aorta was ligated and divided. Immediately after this, in-site flushing was carried out while ventilation was continued. Using this technique, the warm ischemic pe-

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riod was less than 90 seconds. Four hundred milliliters of flushing solution at the predetermined temperature was infused through the pulmonary artery cannula at a height of 60 cm; the effluent was drained through the left ventricular drainage tube. The tubing system for flushing consisted of a standard intravenous set tube of 70 cm, a stopcock (Cobe 11R 9703), and a 5-cm pulmonary artery cannula (Cobe 05P 9290). Duration and pulmonary artery pressure during flushing were recorded for calculating the pulmonary vascular resistance. As soon as the flushing was completed, the left ventricular drainage tube was removed with the ligation of the pursestring suture. Thus, the flushing solution was kept inside the heart-lung block, and isolated from the immersion solution during storage. The right PA and the right main bronchus were ligated after flushing. The average pulmonary vascular resistance (PVR) during flushing was calculated as follows: $PVR \text{ (mm Hg} \cdot \text{L}^{-1} \cdot \text{min)} = [\text{pulmonary artery pressure (mm Hg)} - \text{left atrial pressure (mm Hg)}] / \text{flow rate (L/min)}$. A modified phosphate-buffered extracellular (LPD) solution was used [5]. The composition of the solution was as follows: Na^+ , 168 mmol/L; K^+ , 4.0 mmol/L; chloride, 104 mmol/L; magnesium sulfate, 2.0 mmol/L; phosphate radical, 36.7 mmol/L; low-molecular-weight dextran, 2%; and heparin, 2,000 U/L.

In group I, the heart-lung blocks were harvested without flushing, inflated to tidal volume, and stored at 10°C for 30 hours. The ischemic period before immersion for cool storage in this group ranged from 10 to 15 minutes. For flush preservation (groups II through V), the lungs were flushed in-site at different temperatures (groups II and IV, 10°C; groups III and V, 23°C). They were then harvested, inflated to tidal volume, and stored at 10°C for various ischemic periods (groups II and III, 30 hours; groups IV and V, 36 hours).

For postischemic functional assessment, the left lung was ventilated with room air (rate, 25/min; tidal volume, 15 mL, positive end-expiratory pressure, 0.5 cm H_2O) and perfused with heparinized fresh rabbit venous blood (rate, 40 mL/min) for 10 minutes as previously described [4]. In the present model, unlike our previous report, a spirometer was not used in the ventilatory circuit. Thus oxygen uptake was not measured. The parameters for function assessment included gas analysis of venous perfusate and pulmonary venous effluent blood, $\overline{\text{PAP}}$, and mean airway pressure ($\overline{\text{P}_{\text{aw}}}$). Blood gases of the affluent blood were measured at 5 and 10 minutes; the other parameters were recorded continuously throughout the assessment.

All results were presented as mean $\pm$ standard error of mean. Statistical analysis was performed using the unpaired *t* test. Statistical significance was assumed for a *p* value less than 0.05.

All animals received humane care in compliance with the "Principles of Laboratory Care" formulated by the National Society for Medical Research, and the "Guide for the Care and Use of Laboratory Animals" prepared by National Academy of Sciences and published by the National Institutes of Health (NIH publication No. 85-23, revised 1985).

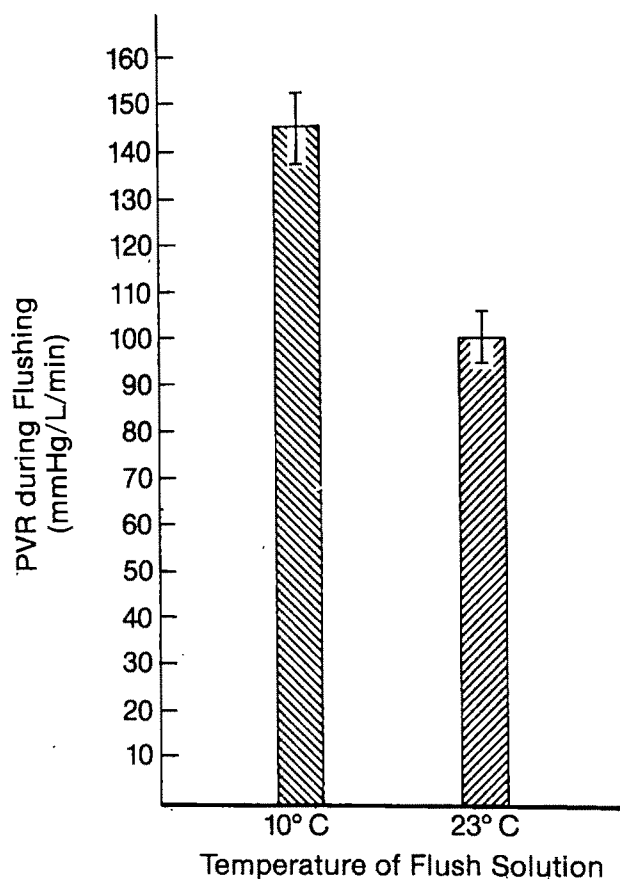


Fig 1. Flushing of lungs with LPD solution at 10°C resulted in a significantly higher pulmonary vascular resistance (PVR) compared with flushing at 23°C ($p < 0.001$).

Results

Venous Perfusate

The gas analysis and the hematocrits of pulmonary artery infusion blood did not differ among all groups. The oxygen tension was 16.5 ± 0.6 mm Hg; carbon dioxide tension, 65.5 ± 3.5 mm Hg; hemoglobin level, 105 ± 3 g/L; and hematocrit, 0.35 ± 0.03 ($n = 25$).

Mean Pulmonary Artery Pressure, Flow Rate, and Pulmonary Vascular Resistance During Flushing

Pulmonary artery pressure in the anesthetized rabbit before flushing was stable and constant (10.8 ± 0.3 mm Hg; $n = 20$). During flushing of the lungs at 23°C, the $\overline{\text{PAP}}$ was 10.7 ± 0.5 mm Hg; flow rate, 119.4 ± 2.0 mL/min; and PVR, 98.4 ± 5.0 mm Hg $\cdot \text{L}^{-1} \cdot \text{min}$ ($n = 10$). At a flushing temperature of 10°C, the $\overline{\text{PAP}}$ during flushing was 13.1 ± 0.5 mm Hg; flow rate, 91.9 ± 2.1 mL/min; and PVR, 144.9 ± 8.7 mm Hg $\cdot \text{L}^{-1} \cdot \text{min}$ ($n = 10$). During flushing at 23°C, the $\overline{\text{PAP}}$ was stable throughout the process, but the $\overline{\text{PAP}}$ at 10°C gradually increased during the initial 1 to 2 minutes of flushing and then became constant. Flushing of lungs at 10°C resulted in a significantly higher PVR compared with flushing at 23°C ($p < 0.001$) (Fig 1).

Table 1. Postischemic Functional Assessments^a

Group	Temperature of Flush Solution (°C)	Ischemic period (h)	PaO ₂ (mm Hg)		PaCO ₂ (mm Hg)		PAP (mm Hg)		P _{aw} (mm Hg)	
			5 min	10 min	5 min	10 min	5 min	10 min	5 min	10 min
I	No flushing	30	67.4 ± 12.5	65.3 ± 8.0	41.4 ± 3.6	39.8 ± 3.3	22.0 ± 2.8	21.4 ± 3.2	2.6 ± 0.9	2.6 ± 0.9
II	10	30	108.7 ± 5.2	95.3 ± 7.0 ^b	30.1 ± 0.8	30.8 ± 0.9 ^b	16.4 ± 0.7	16.4 ± 0.7	2.2 ± 0.1	2.2 ± 0.1
III	23	30	124.9 ± 1.4	120.0 ± 0.9 ^b	30.3 ± 0.6	30.7 ± 0.6	14.0 ± 0.7	13.6 ± 0.5 ^b	2.2 ± 0.1	2.2 ± 0.1
IV	10	36	90.2 ± 14.6	62.5 ± 10.1	33.0 ± 2.6	33.6 ± 2.8	17.8 ± 1.7	19.0 ± 1.9	2.5 ± 0.2	3.5 ± 0.7
V	23	36	104.3 ± 9.1	105.2 ± 7.9 ^b	31.0 ± 0.6	30.5 ± 0.6	13.2 ± 0.6	12.7 ± 0.5 ^b	2.4 ± 0.3	2.7 ± 0.6

^a The lungs in group I (nonflushing group) were preserved only with simple cool (10°C) immersion. The lungs in groups II through V (flushing groups) were flushed in situ at different temperatures and then stored at 10°C for various ischemic periods. All data are presented as mean ± standard error of the mean. ^b $p < 0.05$ versus the group immediately above.

PaCO₂ = arterial carbon dioxide tension; PaO₂ = arterial oxygen tension; PAP = mean pulmonary artery pressure; P_{aw} = mean airway pressure.

Postischemic Pulmonary Functional Assessments

All data of pulmonary venous effluent blood oxygen tension (PaO₂), pulmonary venous effluent blood carbon dioxide tension (PaCO₂), PAP, and P_{aw} are presented in Table 1. The results of PaO₂ and PAP measurements are displayed graphically in Figures 2 and 3.

COMPARISON BETWEEN THE EFFECTS OF COLD FLUSHING AND TOPICAL HYPOTHERMIA. In comparison with the lungs with simple immersion at 10°C for 30 hours (group I), the lungs flushed at 10°C (group II) demonstrated significant improvement in PaO₂ (group I, 65.3 ± 8.0 mm Hg; group II, 95.3 ± 7.0 mm Hg at 10 minutes; $p < 0.05$) (see Fig 2) and PaCO₂ (group I, 39.8 ± 3.3 mm Hg; group II, 30.8 ± 0.9 mm Hg; $p < 0.05$). Higher values of PAP were also found in group I (see Fig 3), but the results obtained at 5 and 10 minutes were not significant compared with group

II ($0.1 < p < 0.05$). The P_{aw} in group I was similar to that in group II.

COMPARISON BETWEEN LUNGS FLUSHED AT DIFFERENT TEMPERATURES. At an ischemic period of 30 hours, for lungs flushed at 10°C (group II) the PaO₂ during perfusion was 95.3 ± 7.0 mm Hg, and PAP was 16.4 ± 0.7 mm Hg at 10 minutes. When the temperature of the flushing solution was 23°C (group III), there was a significant improvement in PaO₂ (120.0 ± 0.9 mm Hg at 10 minutes; $p < 0.05$) and a decrease in PAP (13.6 ± 0.5 mm Hg at 10 minutes; $p < 0.02$) compared with group II. There was no difference in PaCO₂ and P_{aw} between groups II and III.

When the ischemic period was prolonged to 36 hours, the PaO₂ of group V lungs (23°C) showed no significant decrease (105.2 ± 7.9 mm Hg at 10 minutes). Compared with group V, the group IV lungs (10°C) displayed a significant deterioration in PaO₂ (62.5 ± 11.7 mm Hg at 10 minutes; $p < 0.05$). Furthermore, whereas the PAP in group V was 12.7 ± 0.5 mm Hg at 10 minutes, the PAP in group IV was significantly increased to 19.0 ± 1.9 mm Hg at 10 minutes ($p < 0.05$). There was no difference in PaCO₂ and P_{aw} between groups IV and V.

Comment

Currently organ preservation is primarily based on reversible inhibition of the isolated organ's metabolism by

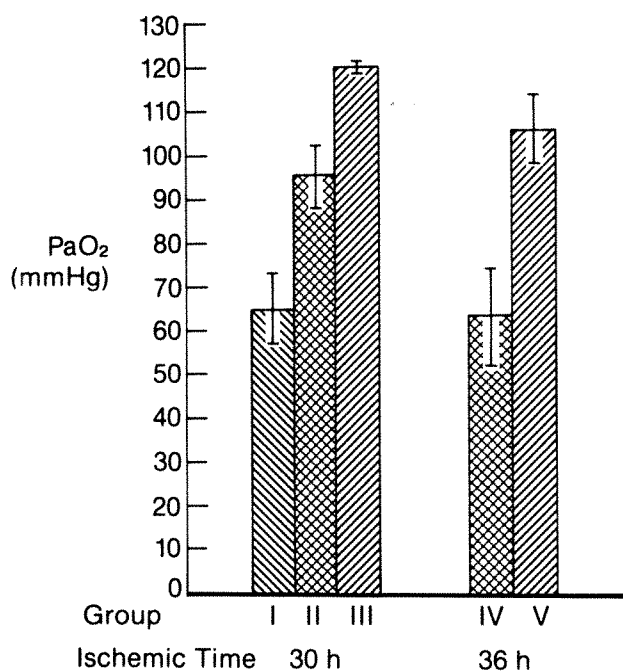


Fig 2. Arterial oxygen tension (PaO₂) of groups I through V at the end (at 10 minutes) of the reperfusion period.

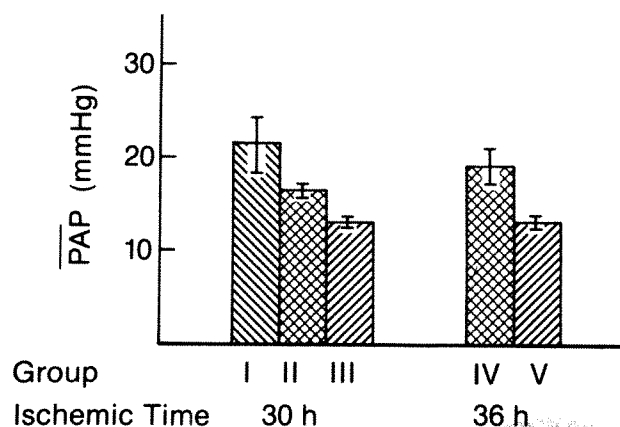
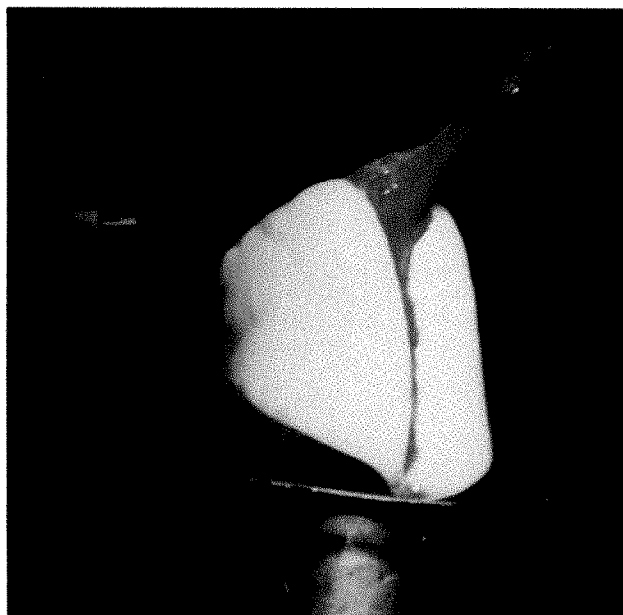
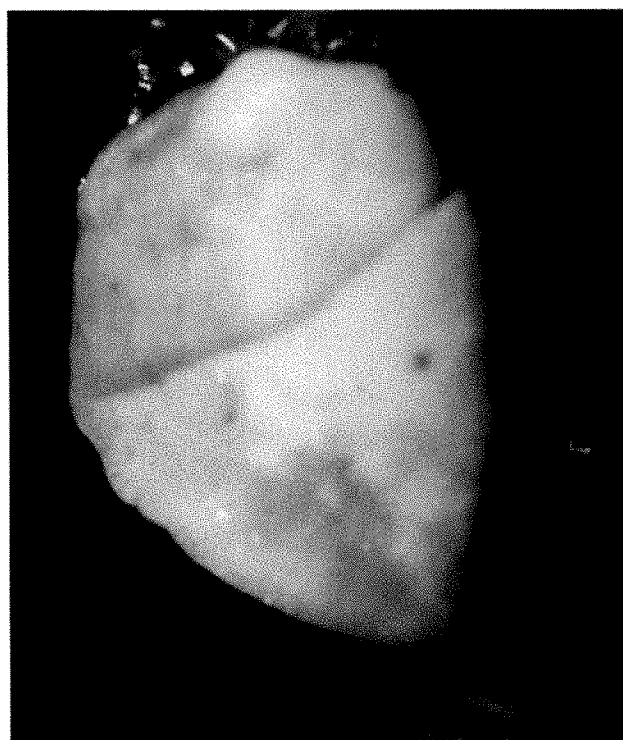


Fig 3. Mean pulmonary arterial perfusion pressure (PAP) of groups I through V at the end (at 10 minutes) of reperfusion.



A



B

Fig 4. (A) Uniform and clean wash-out of the pulmonary vascular bed was easily obtained while the temperature of flushing solution was 23°C. (B) In contrast, it was quite difficult to establish uniform and clean wash-out of the pulmonary vascular bed if the temperature was 10°C.

hypothermia. There are two ways to achieve hypothermia: surface and flush cooling. Surface cooling is an inefficient method for reducing the core temperature of a large organ, especially for inflated lungs with the insulat-

ing effect of air. Inefficient cooling results in a longer period of warm ischemia. The detrimental effects of even a short period of normothermic ischemia on the lungs subsequently preserved by topical hypothermia are well recognized [3, 5, 6]. Moreover, when the blood supply to an organ is terminated, the following occur immediately: decrease in temperature, collapse of vascular system, and stasis of blood, particularly in the capillaries and venous system. Thus, the vasculature of an ischemic organ becomes progressively more difficult to perfuse as the duration of ischemia is prolonged. This is the so-called no-reflow phenomenon, and may be an important contributing factor to warm ischemic injury [7].

Flush preservation of the lungs may provide several advantages: (1) rapid cooling and shortening of the period of normothermic ischemia; (2) washout of pulmonary vascular blood, thus possibly preventing the no-reflow phenomenon and the production of toxic substances from the ischemic blood components; and (3) minimizing the adverse effects of cooling on cell physiology by the use of an appropriate flush solution. However, flushing with a crystalloid solution may, under some circumstances, be harmful if cellular or interstitial edema results.

It has been emphasized that of all the investigations pertinent to flush preservation of lung, none has given consistent and predictable results [2]. This lack of consistency raises the question that some factors, besides the composition of the flushing solution, may contribute to this inconsistency. The effects of temperature and volume of perfusate, flow and pressure during flushing, uniformity of flow distribution, and airway status during flushing have yet to be accurately defined.

Cooling can be immediately produced by a brief flush with a chilled electrolyte solution. However, an ill-understood phenomenon, "thermal shock," may occur whereby some cells are damaged by rapid cooling even without freezing. This phenomenon has long been known to occur in some microorganisms [8], spermatozoa [9], and modified erythrocytes [10]. In relation to organ preservation, Pegg and colleagues [3] have demonstrated a highly deleterious effect of rapid cooling (rate > 7.2 mL/min) in the rabbit kidney. Otto and co-workers [11] concluded that rapid cooling is an important pathophysiological mechanism in porcine liver preservation. Isselhard and his associates have studied skeletal muscle in rats and dogs and found that cooling to 0° to 2°C in 4 minutes impaired both metabolism and survival rate, whereas cooling to the same temperature in 90 minutes had an excellent preservation effect (unpublished results). Moreover, it has also been suggested that a rapid cooling rate might damage rat hearts [12].

From our previous studies [5], we found that the optimal temperature for lung preservation appears to be in the vicinity of 10°C. However, the optimal storage temperature may not necessarily be the optimal flushing temperature. Our results demonstrated that, functionally, the lungs flushed with LPD solution at 23°C were superior to those flushed at 10°C. Flushing of the lungs at low temperatures may cause vasoconstriction with high vascular resistance, thus disturbing the uniformity and com-

pleteness of the blood washout (Fig 4), even after premedication with prostaglandin E_1 . Furthermore, rapid cooling might impair the endothelial function and induce interstitial or cellular edema due to vascular spasm, or other undetermined mechanisms, but dilatation of the smooth muscle bed could occur with prostaglandin E_1 . However, it is difficult to determine whether this is due to a direct temperature effect on lung parenchyma or a vascular effect with a relatively poor quality of flushing.

The rabbit lung is so small that it is rather easy to cool down by immersion in cool solution. By placing a small probe thermometer into the right lung to continuously measure lung temperature, we found that it generally only took 2 to 3 minutes to cool down the rabbit lung from room temperature (23°C) to 10°C. However, for a large animal lung, this temperature change seems to have a different situation. It should take a longer time to cool the lung by simple immersion. Thus, theoretically, it may be advisable to sequentially change the temperature of flushing solution from room temperature (23°C) to the optimal lower temperature. In this way a uniform flushing and a shorter warm ischemic time of the preserved lung may be more easily achieved. However, further studies relative to the amount and compositions of flushing solution and the flow rate and pressure during flushing are also needed.

From this study, we conclude that in lung preservation, uniform flushing with LPD solution improved ischemic tolerance, as compared with simple topical hypothermia, and that flushing of lungs with low-temperature solution is likely to produce rapid cooling and a higher vascular resistance with incomplete blood removal from the ischemic lungs; each of these effects may adversely affect lung preservation.

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Male Donor Into Female Recipient Increases the Risk of Pediatric Heart Allograft Rejection

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Sixty-one infants and children, 12 years old or younger, who received an orthotopic cardiac allograft between November 1985 and December 1989 were analyzed for the incidence of rejection. Rejection was diagnosed non-invasively within the first 3 months and during the first year. Rejection episodes were diagnosed by signs and symptoms according to previously reported criteria. Multiple regression analysis with recipient age, donor age, donor-recipient weight ratio, number of HLA mismatches, sex of the recipient, sex-encoded minor tissue antigen incompatibility (H-Y: female recipients receiving male donor organ), graft ischemic time, lowest cyclosporine level during the first 2 postoperative weeks, and prophylactic use of OKT3 showed that H-Y was the only significant contributing factor for rejection at 3 months and 1 year ($r = 0.308$, $p < 0.02$; $r = 0.308$, $p < 0.02$;

respectively). Patients were divided into two groups: group 1, 45 patients who were H-Y compatible (male and female recipients receiving female donor hearts); and group 2, 16 patients who were H-Y incompatible (female recipients with male hearts). Patients in group 2 had significantly more episodes of graft rejection than did patients in group 1 by 3 months and by 12 months after heart transplantation (3 months: 2.75 ± 1.48 versus 1.67 ± 1.41 , $p < 0.05$; 1 year: 4.80 ± 1.87 versus 2.59 ± 1.93 , $p < 0.01$; respectively). There were six grafts lost due to rejection in group 2 (6/15, 37.5%) and 7 grafts lost (7/45, 15.5%) in Group 1 (not significant). Heart transplantation with H-Y incompatibility resulted in a significantly greater incidence of rejection episodes.

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It is recognized that antigenic differences at the major histocompatibility (MHC) complex play a significant role in clinical and experimental allograft rejection. However, grafts expressing minor non-MHC transplantation antigens may also be at risk for accelerated rejection. Such may be the case with the sex-specific transplantation antigen H-Y, a minor tissue antigen. For example, female mice of some strains reject skin grafts from male donors of the same strain [1-5]. Goulmeyer and co-workers [6, 7] reported the importance of H-Y (sex antigen) incompatibility in human bone marrow transplantation. Crandall and associates [8] reported increased cardiac allograft rejection in female heart transplant recipients, but did not evaluate specific H-Y incompatibility. The effect of recipient sex in clinical kidney transplantation is not clear [9-13]. In this report, we assess the importance of H-Y incompatibility between donor and recipient in pediatric cardiac transplantation.

Material and Methods

Patients

Pediatric patients up to 12 years old who received cardiac allografts between November 1985 and December 1989 at

Loma Linda University Medical Center were retrospectively reviewed. Of 71 patients who received 73 allografts in this period, 10 recipients (11 allografts) who died perioperatively for reasons other than rejection and one retransplantation are not included in this study. This study covers the 61 remaining patients.

The age of the recipients in this study was from 3 hours to 12 years (mean, 13.4 months). The indications for transplantation were hypoplastic left heart syndrome, 37; cardiomyopathy, 11; and other congenital cardiac anomalies, 13.

The surgical procedure, management, and postoperative immunosuppressive therapy are the same as previously reported [14-16]. Briefly, intravenous cyclosporine administration was started 6 hours preoperatively and maintained postoperatively at 0.1 mg/kg per hour. When oral feedings were well tolerated, intravenous administration of cyclosporine was discontinued and oral administration (4 to $15 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ in divided doses every 8 to 12 hours) was started. Azathioprine at $3 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ was also administered intravenously or orally. Corticosteroids were prescribed for 2 days perioperatively and for treatment of acute rejection episodes, which were diagnosed according to previously reported criteria using echocardiography, chest roentgenography, and clinical examination or suspicion [17]. Endomyocardial biopsies were used selectively in older children. Rejection episodes were initially treated with oral or intravenous administra-

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tion of steroids. Antithymocyte globulin or OKT3 was administered for recurrent or for moderate to severe episodes. One young infant underwent successful retransplantation after rejection-induced acute failure of his primary graft.

Twelve patients died 4 months to 3 years after transplantation due to acute or chronic rejection.

Study Methods

Recipient age, donor age, donor/recipient weight ratio, number of HLA antigen mismatches, sex of the recipient, Y-chromosome incompatibility (H-Y), graft ischemic time, lowest cyclosporine level (postoperative day 0 to 14), and prophylactic use of OKT3 were retrospectively reviewed. The analysis attempted to detect correlation of any of the above parameters with the number of treated rejection episodes within the first 3 months and within the first year. Rejection episodes were defined as occurring whenever echocardiographic, clinical, or biopsy signs of rejection were actively treated or were found at autopsy. Multivariate regression analysis was employed for statistical assessment. No organs were transplanted across ABO blood group barriers, and no patient was presensitized to the specific donor. The 61 patients were divided into two groups: group 1, 45 patients without H-Y incompatibility (all male recipients and female recipients with female donor hearts); and group 2, 16 patients with H-Y incompatibility, ie, female recipients with male hearts. Rejection episodes at 3 months and 1 year and number of graft losses from rejection were compared between the groups. Additional statistical analysis included Student's *t* test and the χ^2 test. A *p* value less than 0.05 was considered to be significant.*

Results

Multiple regression analysis using the independent variables described in the previous section indicated that H-Y incompatibility was the only significant contributing factor to rejection at 3 months or 1 year ($r = 0.308$, $p < 0.02$; $r = 0.308$, $p < 0.02$; respectively). Equally important, we found no correlation between recipient age, donor age, donor/recipient weight ratio, number of HLA mismatches, sex of the recipient, graft ischemic time, low cyclosporine level, and prophylactic use of OKT3.

Patients with H-Y incompatibility (male donors into female recipients; group 2) showed significantly greater numbers of rejection episodes than those with H-Y compatibility (group 1). This was not only true during the first 3 months (episodes of rejection: 2.75 ± 1.48 versus 1.67 ± 1.41 , respectively; $t = 2.59$, $p < 0.05$) but also during the first year (4.80 ± 1.87 versus 2.59 ± 1.93 ; $t = 3.00$, $p < 0.01$). There were 6 graft losses from rejection in group 2 (6/16, 37.5%) and 7 graft losses (7/45, 15.5%) in group 1. This difference did not reach statistical significance ($\chi^2 = 3.39$).

* Statistics in this study were consulted with Grenith Zimmerman, PhD, Professor of Biostatistics, School of Allied Health Professions, Loma Linda University, Loma Linda, CA.

Comment

It is widely accepted that female sex is a risk factor in several autoimmune diseases including systemic lupus erythematosus and thyroiditis. Before this study, we had anecdotally suspected that female sex was a risk factor for increased frequency of rejection in our pediatric heart transplant population. Indeed, it appears as though our impressions were correct, as female pediatric recipients of hearts do have more rejection episodes than other recipients. However, our study suggests that this conclusion is too simplistic, and this retrospective study illustrates that, in the pediatric population, H-Y incompatibility (male hearts into female recipients) accounts for this phenomenon. Recipient sex, per se, was not an independent variable favoring increased rejection, but the large number of female recipients of male donor hearts tipped the overall balance so that it appeared that female sex was an independent risk factor in this very early age group. But, among only female recipients, those with male hearts had more rejection episodes than those with female hearts (2.75 ± 1.48 versus 2.0 ± 2.0 within 3 months; 4.80 ± 1.87 versus 2.25 ± 3.20 within 1 year). This did not reach statistical significance because the number of female recipients with female donor hearts was small ($n = 5$).

Female sex as an independent variable did not reach statistical significance in the present study. Early age at the time of transplantation, with its implied lack of immunologic experience, may account for this finding. Older female patients with mature immunological response appear, in fact, to more aggressively reject their transplanted organ. In bone marrow transplantation, Goulmy and associates [7] reported that peripheral blood lymphocytes of an aplastic anemia patient with an H-Y incompatible donor bone marrow transplant were able to show HLA-restricted H-Y killing in a cell-mediated lymphocyte assay. A high incidence of female donor cell reactions to recipient H-Y antigen in HLA-matched bone marrow transplantation was also observed in the early postoperative period [18]. Sex matching of the donor and recipient was also considered to have a significant bearing on the survival of patients with aplastic anemia who received marrow transplantation from HLA-identical siblings [19].

Male-specific antigen is also considered to be an important histocompatibility antigen in clinical kidney transplantation when donor and recipient are HLA identical, or both are HLA-A2 positive [7, 9]. Conversely, Opelz and Terasaki [13] could find no donor sex-related difference in survival of kidney grafts. Indeed, maternal recipients of kidney grafts from their children showed better results than paternal recipients, although this may be the result of immunological moderation from pregnancy.

The number of HLA mismatches clearly influences the results of transplantation among male kidney recipients, especially non-O blood type individuals. The influence of these factors is further altered by multiple transfusions [13]. Kidney grafts from male donors into multiparous female recipients survived longer, but male grafts into nulliparous females did not [11]. Similarly, pregnancy in

inbred mice is associated with long-term acceptance of H-Y incompatible skin grafts, even in some "rejecter" strain females [20]. Thus, the importance of the H-Y minor antigen mismatch in renal transplantation may be obscured by more powerful transplantation antigens.

Crandall and co-workers [8] reported increased cardiac allograft rejection in female patients in a series of 140 heart transplant recipients. No differences were observed in mortality, but rejection episodes in the first 4 months were significantly more frequent in female recipients. They attributed those observations to (1) the possibility that the female possesses an intrinsically more vigorous immune system and (2) the possibility that these findings may be specific for immunosuppressive protocols that eliminate maintenance corticosteroids. They suggested that sex-related difference became less apparent when all recipients received maintenance corticosteroid therapy. Moreover, in adults, especially in adult kidney transplant recipients as mentioned above, pregnancy and multiple transfusions may modify the outcome.

In our series of pediatric patients, steroids were administered immediately postoperatively and then only for rejection episodes. This lack of broad immunosuppression by steroids may have allowed expression of immune response to less important transplantation antigens, such as the Y antigen mismatch. The antibody titer for male-specific antigen decreases at about 1 year after transplantation [7]. Thus, H-Y incompatibility may only influence the occurrence of graft rejection in the early transplant period. Indeed, rejection episodes are extremely rare more than a year after transplantation in both male and female patients in our population. Importantly, weak transplantation antigens, such as male-specific antigen, do not usually result in differences in mortality. Although we observed a difference in mortality that might be attributed to sex disparity, this difference has yet to reach statistical significance. For this reason, we have not routinely strengthened the immunosuppressive regimen in female patients receiving male donor hearts. Although the addition of steroids may blunt much of their additional rejection risks, maintenance steroids carry such long-term morbidity in infants and children that we continue to avoid their use whenever possible.

Finally, a potential weakness of this study is the use of the treatment of a suspected rejection episode as an objective measure of rejection. Although seemingly less concrete than an endomyocardial biopsy, we have previously shown an extremely strong correlation of the clinical suspicion of rejection by echography and physical/laboratory examination to endomyocardial biopsy [16]. Particularly in this population, in which repeated venous access is limited, the thoroughness with which rejection is sought for clinically justifies this technique as a measurement of rejection episodes.

In conclusion, based on our study of 61 infant and pediatric heart transplant recipients, we have found that a mismatch of the Y antigen (H-Y incompatibility) that occurs when a male donor heart is transplanted into a

female recipient significantly increases the number of rejection episodes during the first 3 months and 1 year after transplantation. Although there is a suggestion that late mortality is also increased in patients with this mismatch, this conclusion must await a larger patient volume and follow-up. Because of the very contracted donor pool, we continue to place male hearts into female recipients, but these children are monitored closely and treated aggressively for rejection.

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Severe Ischemic Left Ventricular Failure: Coronary Operation or Heart Transplantation?

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Severe left ventricular failure in ischemic heart disease may contraindicate conservative surgical procedures. To redefine therapeutic indications, the clinical and angiographic data of 143 patients (137 men and 6 women) with ischemic heart disease and a left ventricular ejection fraction less than 0.30 who were seen by us between June 1985 and December 1990 were retrospectively analyzed. Patients were divided into three groups according to therapy: medical only, 72 (group 1); myocardial revascularization, 20 (group 2); and heart transplantation, 51 (group 3). Clinical status was poorer in group 3, with congestive heart failure as predominant symptom; angina was more frequent in group 2. No difference was noted in hemodynamic variables. Four early deaths

(20.0%) occurred in group 2 and 7 (13.7%) in group 3. Follow-up ranged from 1 to 64 months (mean, 22 ± 19 months), with an actuarial survival of $28\% \pm 9\%$, $80\% \pm 8\%$ and $82\% \pm 5\%$ at 5 years in groups 1, 2, and 3, respectively. Even though postoperative New York Heart Association class was better in group 3 (1.0 versus 2.3 in group 2; $p < 0.01$), the difference in survival was not significant. Although in patients with ischemic heart disease and low left ventricular ejection fraction heart transplantation offers the best clinical results, considering the donor shortage, we conclude that myocardial revascularization may still be performed with good mid-term results.

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Heart transplantation (HTx) has gained widespread acceptance as a valid therapeutic alternative for patients with end-stage ischemic heart disease [1]. The improvement in survival and quality of life after heart transplantation, mainly due to safer immunosuppression and better patient management, has led to a steady growth of the recipient pool [1]. Unfortunately, the number of available donors has remained chronically insufficient [2] and, currently, more than 35% of the heart transplant candidates die while on the waiting list [3].

Myocardial revascularization has also benefited from improved technological advances and patient management, likewise resulting in improved survival [4]. Thus, patients previously considered at prohibitive risk for

clinical and angiographic variables, we attempt to identify criteria that might be useful in selecting patients either for conservative operation or for HTx.

Material and Methods

From June 1985 to December 1990, 143 patients with ischemic cardiomyopathy were referred to our institution. All had angiographic evidence of multiple critical coronary lesions and a left ventricular ejection fraction (LVEF) less than 0.30; patients with left ventricular aneurysm were excluded from this study. The 137 men and 6 women were divided into three groups according to the type of therapy: 72 patients received medical therapy only (group 1), 20 underwent myocardial revascularization (group 2), and 51 had HTx (group 3). The patients in group 1 included 45 patients referred for HTx and 27 patients belonging to a cardiological series, for whom only medical treatment was initially advised; 20 of these patients were subsequently offered CABG but refused this option. The remaining patients were nonrandomly distributed between groups 2 and 3.

The clinical profile of patients is illustrated in Table 1. Although age and sex of the patients in the three groups were comparable, group 3 patients were in significantly poorer clinical condition compared with patients in the other groups. The predominant symptom was also different among patients: severe angina refractory to medication was significantly more frequent in group 2 ($p < 0.01$), whereas congestive heart failure was more common in group 3 ($p < 0.01$). Ventricular arrhythmias (including multiple premature complexes, tachycardia, and ventric-

For editorial comment, see page 581.

surgical revascularization may undergo coronary artery bypass grafting (CABG) with low operative mortality and a successful long-term outcome [4, 5]. Therefore, a definition of the selection criteria of patients with end-stage ischemic heart disease for either myocardial revascularization or HTx has become increasingly important. In this article, we present the midterm clinical results obtained in three groups of patients with ischemic heart disease and severe left ventricular failure (ejection fraction < 0.30) who were treated with medical therapy only, revascularization, or HTx. Moreover, by retrospective analysis of

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Table 1. Clinical Profile of Patients^a

Variable	Group 1 (n = 72)	p Value (1 vs 2)	Group 2 (n = 20)	p Value (2 vs 3)	Group 3 (n = 51)	p Value (3 vs 1)
Age (y)						
Mean	56 ± 9	NS ^b	56 ± 8	NS ^b	53 ± 7	NS ^b
Range	30-71		43-75		36-64	
Sex (M/F)	70/2	NS ^c	18/2	NS ^c	49/2	NS ^c
Mean NYHA class at admission	3.1 ± 0.6	NS ^b	3.2 ± 0.4	<0.01 ^b	3.8 ± 0.4	<0.01 ^b
Arrhythmias (% of patients)	51	<0.01 ^c	25	<0.01 ^c	43	NS ^c
Angina (% of patients)	43	<0.01 ^c	70	<0.01 ^c	35	NS ^c
CHF (% of patients)	55	NS ^c	46	<0.01 ^c	80	<0.01 ^c
Follow-up (mo)						
Mean	20 ± 17	<0.01 ^d	34 ± 24	<0.01 ^d	21 ± 16	NS ^d
Range	1-64		1-64		1-64	

^a Values are shown as mean ± standard deviation. ^b Student's *t* test. ^c Pearson's χ^2 test. ^d Wilcoxon rank-sum test.

CHF = congestive heart failure; NS = not significant; NYHA = New York Heart Association.

ular fibrillation) were documented by electrocardiography in about half of the patients in groups 1 and 3, being less frequent in group 2 ($p < 0.01$).

Angiographic data at admission are summarized in Table 2. The extent of left ventricular failure is evidenced by the low LVEF, the large left ventricular end-diastolic volume, and the high mean pulmonary artery pressure in all groups. None of the variables analyzed was significantly different between groups.

The majority of group 1 patients were receiving digitalis in association with either diuretics (55%) or vasodilators, including nitrates (35%); few patients (<10%) were receiving vasodilators only.

Five patients (25%) in group 2 were on intravenous inotropic support or an intraaortic balloon pump preoperatively. All patients in group 2 underwent CABG, with a mean number of 2.2 grafts per patient. In 30% of patients CABG was associated with other surgical procedures: postinfarction ventricular septal defect repair in 3 patients (15%), mitral valve annuloplasty in 2 (10%), and mitral valve replacement in 1 (5%).

Surgical therapy in group 3 included orthotopic HTx in 44 patients and heterotopic HTx in 7. Twelve of these

patients (24%) had previous operations: CABG (10 patients) and CABG associated with mitral valve annuloplasty (2 patients). Only 3 patients (6%) required intravenous inotropic support or mechanical assist before transplantation.

Midterm cardiac function was assessed by means of clinical examination (New York Heart Association [NYHA] functional class at follow-up) and mean LVEF at last follow-up echocardiography in all patients. Because all patients undergo angiography on a yearly basis after HTx, angiographic data were also available in group 3.

Standard statistical methods used included Student's *t* test for paired and nonpaired data for comparison of continuous variables, Pearson's χ^2 for discrete variables, and the Wilcoxon rank-sum test for follow-up periods. The Kaplan-Meier method and the corresponding log-rank test were used for survival, whereas univariate (χ^2 and Wilcoxon rank-sum) analysis was used to identify variables predictive of mortality. The variables tested included age, sex, NYHA class, angina, congestive heart failure, LVEF, left ventricular end-diastolic volume, cardiac index, pulmonary artery pressure, and therapy. A value of *p* less than 0.05 was considered significant.

Table 2. Angiographic Data at Admission^a

Variable	Group 1 (n = 72)	p Value (1 vs 2)	Group 2 (n = 20)	p Value (2 vs 3)	Group 3 (n = 51)	p Value (3 vs 1)
LVEF	0.21 ± 0.06	NS ^b	0.22 ± 0.08	NS ^b	0.23 ± 0.07	NS ^b
LVEDV (mL)	158 ± 49	NS ^b	162 ± 70	NS ^b	168 ± 60	NS ^b
CI (L · min ⁻¹ · m ⁻²)	2.3 ± 0.9	NS ^b	2.1 ± 0.4	NS ^b	2.1 ± 0.6	NS ^b
PAP (mm Hg)	34 ± 13	NS ^b	32 ± 12	NS ^b	39 ± 15	NS ^b
No. vessels involved	2.3 ± 0.7	NS ^b	2.5 ± 0.7	NS ^b	2.5 ± 0.6	NS ^b
Mitral regurgitation (% of patients)	31%	NS ^c	35%	NS ^c	40%	NS ^c

^a All values are shown as mean ± standard deviation. ^b Student's *t* test. ^c Pearson's χ^2 .

CI = cardiac index; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; mitral regurgitation = mild to moderate insufficiency; NS = not significant; PAP = mean pulmonary artery pressure.

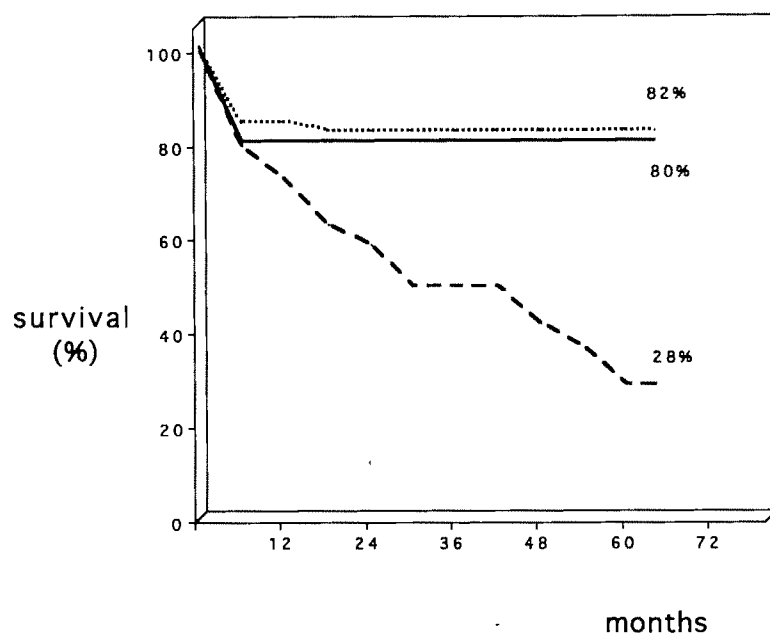


Fig 1. Actuarial survival of patients with severe ischemic left ventricular failure according to type of treatment. The dotted line depicts survival of patients undergoing heart transplantation (51); the solid line, survival of patients undergoing myocardial revascularization (20); and the broken line, survival of patients receiving medical therapy only (72). The percentage numbers at the end of each line represent actuarial survival for each group of patients at follow-up (64 months).

Results

Survival

There were 38 deaths in group 1 throughout follow-up; 19 (50%) were in patients referred for HTx who died on the waiting list. All deaths were of cardiac origin. Although 14 deaths were sudden, likely due to malignant ventricular arrhythmias, 20 were the result of either congestive heart failure or infarction; in 4 patients the cause of death was unknown.

There were four (20.0%) (70% confidence interval, 10% to 33%) early deaths (within 30 days of operation) in patients undergoing myocardial revascularization. All deaths occurred perioperatively, due to low output syndrome in critical patients on inotropic or intraaortic balloon pump support preoperatively. In 2 of these patients CABG was associated with repair of a large postinfarction ventricular septal defect. There were no deaths among the 3 patients undergoing CABG and mitral valve operation. Thus, the overall mortality of patients undergoing CABG without associated procedures was 14.3%, whereas the mortality in the group of patients having CABG and ancillary procedures reached 33.3%. Four additional patients required an intraaortic balloon pump postoperatively and were successfully weaned from it. No late deaths occurred in group 2 during follow-up. There were seven (13.7%) (70% confidence interval, 9% to 20%; group 2 versus group 3, $p =$ not significant) early deaths among the transplant recipients; six deaths (11.6%) (70% confidence interval, 7 to 18) occurred perioperatively. The cause of death was acute graft failure in 3 patients, right ventricular failure in the presence of high pulmonary vascular resistance in 2, and acute rejection in 1. One patient died at home suddenly 2 weeks after successful HTx. There was only one late death in group 3; it was caused by chronic rejection 15 months after HTx. No difference was noted between mortality after orthotopic HTx (13.6%; 6/44) and mortality after heterotopic HTx (14.3%; 1/7; $p =$ not significant).

Group 1 patients had a mean follow-up of 20 ± 17 months (range, 1 to 64 months) with an actuarial survival of $28\% \pm 9\%$ at 5 years. Group 2 patients had a mean follow-up of 34 ± 24 months (range, 1 to 64 months) with an actuarial survival of $80\% \pm 8\%$ at 5 years. Group 3 patients had a mean follow-up of 21 ± 16 months (range, 1 to 64 months) with an actuarial survival of $82\% \pm 5\%$ at 5 years. Although the difference in survival between patients receiving medical therapy and patients undergoing cardiac operation was highly significant ($p < 0.001$), no difference was found between conservative operation and heart transplantation (Fig 1).

Retrospective analysis of clinical and angiographic variables demonstrated that the type of treatment was the only variable that was predictive of mortality when the three groups were compared.

Midterm Cardiac Function

Current clinical status was assessed in all groups. Cardiac function of survivors in the medical group had deteriorated at follow-up: whereas 17% of patients were in NYHA class IV and 70% in class III at admission, 90% of them were in class IV and only 10% in class III at follow-up. The mean NYHA functional class was significantly higher when compared with the value at the beginning of the study and with the values in the other groups (Table 3). Progression of the disease was also documented by the decrease in mean LVEF at last echocardiography (Table 4).

The clinical condition significantly improved after myocardial revascularization; only 33% of patients were in NYHA class III and 67% in class II postoperatively, as opposed to 10% in class IV and 85% in class III at admission. Although most patients remained mildly symptomatic and their cardiac function was mildly depressed, the mean postoperative NYHA class and the mean LVEF evidenced a significant improvement from preoperative condition (see Tables 3, 4).

Table 3. NYHA Functional Class at Follow-up^a

Variable	Group 1 (n = 72)	p Value (1 vs 2)	Group 2 (n = 20)	p Value (2 vs 3)	Group 3 (n = 51)	p Value (3 vs 1)
NYHA class begin FU	3.1 ± 0.6	NS	3.2 ± 0.4	<0.01	3.8 ± 0.4	<0.01
p Value (begin vs end FU)	<0.01		<0.01		<0.01	
NYHA class end FU	3.9 ± 0.5	<0.01	2.3 ± 0.6	<0.01	1.0 ± 0.1	<0.01

^a All values are shown as mean ± standard deviation; p values were determined by Student's *t* test.

FU = follow-up; NS = not significant; NYHA = New York Heart Association.

The best functional results were obtained with HTx: 77% of patients were in NYHA class IV and 33% in class III before HTx and all of them shifted to class I postoperatively. Mean post-HTx NYHA class favorably compared with the pretransplantation value and with the postoperative class after CABG (see Table 3). Angiography was performed in 39, 28, 19, and 9 patients at 1, 2, 3, and 4 years after HTx, respectively. All patients but 1 were free of chronic rejection at follow-up, with a mean LVEF of 0.64 ± 0.05 , 0.62 ± 0.04 , 0.63 ± 0.06 , and 0.62 ± 0.07 at 1, 2, 3, and 4 years, respectively. The last echocardiographic examination in all patients showed a normal mean LVEF, significantly improved from the pretransplantation value (see Table 4).

Comment

The validity of HTx as therapeutic alternative for patients with end-stage ischemic heart disease is well established [1]. The success of transplantation occurred as a result of the introduction of cyclosporine in clinical practice, improvements in the selection of recipients and donors, and better management of the complications of immunosuppression [1, 6]. The excellent clinical results of this procedure favored a substantial expansion of the selection criteria for recipients [1]. Thus, in spite of the limited availability of donors, a great increase in the number of transplant candidates ensued [3]. Currently, more than 35% of patients die while waiting for a suitable donor [3]. Along with transplantation, the results of myocardial revascularization have also benefited from improved patient management and surgical techniques [4]. Myocardial revascularization has been shown to dramatically improve early and late survival in patients with severe left ventricular dysfunction [5, 7-10]. Regional ventricular function has also been found to improve after revascularization [11]. To optimize the donor pool and to give patients with nonischemic end-stage cardiac disease a better chance for

transplantation, the therapeutic indications for patients with severe ischemic ventricular dysfunction need to be defined.

Our experience shows that in patients with ischemic heart disease and depressed LVEF medical therapy only offers very poor results. The results presented here demonstrate higher survival when compared with the data published by Franciosa and associates [12] and by Wilson and colleagues [13] on prognosis of patients with end-stage heart disease. Consequently, it might be argued that not all medically treated patients were potential candidates for transplantation at admission in the study. However, it has been shown that many patients with "insufficient" symptoms for HTx still have a very dim outlook: indeed, arrhythmias were found to be a poor prognostic sign in patients with cardiomyopathy [14, 15]. Accordingly, the midterm survival of our medical series substantially agrees with recent works by Harris and co-workers [17] and by Califf and associates [17] showing a 5-year survival rate of about 30% in patients with severe ischemic left ventricular failure assigned to medical therapy. Furthermore, the absence of a significant difference in quantitative angiographic data between groups indicates that the majority of group 1 and group 2 patients might have been candidates for cardiac transplantation. Besides therapy, no clinical or angiographic variable was found to correlate with higher mortality in the medically treated patients.

Myocardial revascularization in patients with severe left ventricular failure yielded good midterm survival and acceptable functional results. Operative mortality seemed higher in our series when compared with the large randomized studies on coronary artery operation [5, 9, 10]. However, none of these studies considered revascularization in patients with severe ventricular failure who also needed associated surgical procedures (mitral valve repair or replacement, repair of a ventricular septal defect). The need for associated cardiac procedures and the poor

Table 4. Cardiac Function at Follow-up^a

Variable	Group 1 (n = 72)	p Value (1 vs 2)	Group 2 (n = 20)	p Value (2 vs 3)	Group 3 (n = 51)	p Value (3 vs 1)
LVEF begin FU	21 ± 6	NS	22 ± 8	NS	23 ± 7	NS
p Value (begin vs end FU)	<0.05		<0.01		<0.01	
LVEF end FU	17 ± 8 ^b	<0.01	42 ± 9 ^b	<0.01	63 ± 6 ^b	<0.01

^a All values are shown as mean ± standard deviation; p values were determined with Student's *t* test. The remaining by angiography.

^b These data were obtained by echocardiography;

FU = follow-up; LVEF = left ventricular ejection fraction; NS = not significant.

preoperative clinical conditions are recognized incremental risk factors for operative mortality [18]. Accordingly, half of our operative deaths occurred in patients undergoing CABG and repair of a ventricular septal defect; in addition, all patients who died early were on an intraaortic balloon pump preoperatively. In fact, our survival data favorably compare with the reported results of myocardial revascularization in high-risk patients awaiting HTx [18-21]. Functional outcome after CABG was acceptable in our series: even if clearly poorer than after transplantation, clinical condition significantly improved after revascularization. Analysis of preoperative variables showed that the predominant symptom in these two groups of patients differed: angina refractory to medical therapy was more common in group 2 and congestive heart failure in group 3. These findings support previous evidence showing that in patients with poor left ventricular function preoperative angina might predict a good result after CABG [8, 20, 22]. Further, considering that the presence of angina in patients with ischemic cardiomyopathy suggests the existence of viable myocardium [22], these results also agree with those by Louie and co-workers [21], who showed that reversible myocardial ischemia at positron emission tomography predicts successful revascularization. Indeed, our limited series indicates that in the presence of bypassable vessels, angina may be the single most reliable criterion to assign patients with ischemic end-stage heart failure to revascularization rather than HTx.

Even though HTx yielded the best survival and functional results, it must be emphasized that as many as 19 patients with severe ischemic left ventricular failure who were initially referred for HTx (10% of all patients enlisted for HTx) died while on the waiting list during the study. Thus, the good midterm outlook after HTx should always be weighed against the limited donor availability [3]. In conclusion, although medical treatment alone bears high mortality in patients with ischemic left ventricular failure and should be reserved only for patients with absolute contraindications to CABG or HTx, revascularization and transplantation offer good and comparable midterm survival. Although operative mortality of conservative cardiac operation is higher and functional results are poorer when compared with HTx, particularly considering the current shortage of donors, all patients with ischemic heart disease and severe left ventricular failure with angina as a leading symptom should be evaluated for myocardial revascularization as an initial procedure.

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Cardiopulmonary Bypass and Pulmonary Thromboxane Generation

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Sporadic cases of inexplicable noncardiogenic pulmonary edema occur after operations requiring total cardiopulmonary bypass (CPB). Prostaglandins, such as thromboxane (Tx) A_2 , have been implicated in this form of pulmonary pathology in many clinical and experimental settings. Because Tx generation has been demonstrated in association with ischemia of solid organs, we postulated that total CPB, which decreases pulmonary tissue perfusion and oxygenation, would stimulate local Tx synthesis. Total CPB was examined in 7 sheep. The level of TxB_2 (a stable metabolite of the active, unstable A_2) was measured in the left and right atria before, during, and after 105 minutes of total CPB. Significant increases in TxB_2 concentrations occurred in the left atrium compared with the right ($p < 0.05$) during CPB. Immediately after reperfusion, both the left atrial and right atrial TxB_2 concentrations increased significantly over the baseline values ($p < 0.05$), but this increase and the atrial gradient

were rapidly abolished with continued pulmonary perfusion. To determine the effect of extracorporeal circulation without significant ($<30\%$) alteration in pulmonary perfusion, we evaluated the effect of partial CPB in 5 sheep. Increased TxB_2 concentrations were noted at 15 and 30 minutes after the onset of partial CPB (left atrium increased significantly over baseline; $p < 0.05$), but this elevation spontaneously diminished to insignificance after 15 and 30 additional minutes of extracorporeal circulation. These data establish that total CPB stimulates Tx generation in the lung, and although the effect of partial CPB is transient, that of total CPB is progressive and abolished by reperfusion. Although the local pathophysiological effects of pulmonary Tx generation after CPB remain to be determined, this study may provide insight into a mechanism for sporadic, noncardiogenic pulmonary edema after CPB.

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Arachidonic acid derivatives, including thromboxane (Tx), are being implicated increasingly as important mediators and modulators of pathophysiological processes in the lungs [1]. Cardiopulmonary bypass (CPB) is associated with an increase in systemic Tx levels [2], but the site and cause of its synthesis in this situation are speculative and have not been rigorously investigated.

Total CPB, as used clinically, results in nearly complete diversion of pulmonary blood flow and the cessation of ventilation. The absence of these two sources of oxygen makes the lung tissue dependent on the variable supply from the bronchial arteries during CPB. Although the oxygen requirement of lung tissue is not great during this time, the lack of pulmonary blood flow might have significant pathophysiological effects. Ischemia is known to stimulate Tx production from other tissues [3, 4], and lungs are a known rich source of this substance [5, 6]. We hypothesized that during total CPB Tx is generated by the lungs rendered ischemic because of their circulatory exclusion and nonventilation.

Material and Methods

Anesthesia and Operation

Dorset-Rambouillet cross-breed female sheep ($n = 12$) weighing 27 to 37 kg (mean weight, 31.5 kg) were premedicated with atropine and anesthetized with intravenous α -chloralose, 80 mg/kg, and urethane, 500 mg/kg. Animals were intubated and mechanically ventilated (Harvard apparatus, Millis, MA). Arterial blood gas and pH were measured during the procedure (pH Blood gas analyzer 1306; Instrument Lab, Lexington, MA) and maintained within physiological limits (pH, 7.35 to 7.42; 100 mm Hg $<$ oxygen tension $<$ 300 mm Hg; 35 mm Hg $<$ carbon dioxide tension $<$ 45 mm Hg). Systemic arterial and central venous pressures were monitored by percutaneous cannulation of the femoral artery and internal jugular vein. In one group of animals ($n = 7$) a left thoracotomy was performed and the main bronchoesophageal artery was identified [7, 8] and isolated. A sternotomy was then performed, and after systemic heparinization (400 IU/kg), cannulas were placed in the right atrium and aorta in preparation for cardiopulmonary bypass. Large-bore catheters were introduced into the left and right atria so that paired, serial samples could be drawn for determination of TxB_2 (a stable, inactive metabolite of the physiologically active but unstable TxA_2) concentration. The extracorporeal circuit consisted of a roller pump

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(Cardiovascular Instrument Corp, Wakefield, MA), and bubble oxygenator (Bentley Bio-2; Baxter Health Care Corp, Irvine, CA). The circuit was primed with Ringer's lactate solution (25 mL/kg).

Animals were cared for in accordance with the guidelines established by the Beth Israel Hospital's Committee on Animal Research and those prepared by the Committee on the Care and Use of Laboratory Animals of the Institute of Animal Resources, National Research Council (DHHS publication No. 85-23, revised 1985). The Beth Israel Hospital animal research facility is fully accredited by the AAALAC.

Experimental Groups

The study consisted of two experimental groups. In the first group (total CPB group), the effect of CPB-induced ischemia of the lungs on TxB_2 profile across the pulmonary circuit was examined. Subsequently, in a second group of animals (partial bypass group), the change in TxB_2 levels was examined during an identical period of extracorporeal circulation, with a minimal degree of pulmonary ischemia (maintenance of >70% pulmonary arterial flow).

TOTAL CARDIOPULMONARY BYPASS GROUP ($n = 7$). In this group, animals were placed on total CPB and, after initial stabilization, the pulmonary artery was clamped and ventilation was halted. Arterial flow was maintained at 80 to 100 $\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and regular blood gas analysis was performed to assess the adequacy of perfusion and gas exchange. Paired serial samples were taken from the left atrium and the right atrium for Tx assay 15, 30, 45, and 60 minutes after commencement of CPB. For the purpose of comparison, simultaneous samples were also obtained from the aortic cannula at different intervals during this period. Thereafter, the bronchial artery was clamped. No sampling was done during this time as left atrial blood return decreased to a minimal level. After 45 minutes of bronchial artery occlusion, CPB was terminated, pulmonary and bronchial artery clamps were removed, and ventilation was resumed. Serial paired samples were taken from the left and right atria immediately and at 10, 25, and 50 minutes after pulmonary reperfusion.

During total CPB and before bronchial artery occlusion, the volume of blood returning to the left heart was measured by placing a wide-bore catheter in the left ventricular cavity. This gave an estimate of bronchial flow in each animal.

PARTIAL CARDIOPULMONARY BYPASS GROUP ($n = 5$). In this group, animals were placed on CPB as above, but less than a third (25 mL/kg) of estimated cardiac output was allowed to flow through the extracorporeal circuit. Partial bypass was achieved by setting a previously calibrated roller pump to the desired output (25 mL/kg). Gravity-assisted venous return was controlled by adjusting the height of draining reservoir (bubble oxygenator) to equal the pump output. Because most of the venous return was allowed to flow through the pulmonary artery and the lungs were ventilated normally, there was no significant

pulmonary ischemia. Paired serial samples were collected from the right and left atria 15, 30, 45, 60, and 90 minutes after the onset of extracorporeal circulation. Cardiopulmonary bypass was then terminated and paired samples were again taken from the right and left atria immediately and at 10, 25, and 50 minutes after termination of bypass.

Sample Collection and Thromboxane Assay

Samples were collected by gentle aspiration from large-bore catheters placed in both atria; the initial 5 mL was discarded to account for dead space. Two-milliliter samples were placed in ice-cooled siliconized tubes containing 100 μL of 0.1 mol/L EDTA and 0.05% (wt/vol) aspirin in a ratio of 2:1. The hematocrit was measured in each sample to permit correction for hemodilution. Samples were immediately centrifuged at 4°C for 20 minutes at 2,000 g. Plasma was separated and stored in polypropylene test tubes at -25°C till assayed. All TxB_2 assays were performed within 2 weeks of experiment. Prior viability studies had shown no significant change in Tx levels for up to 8 weeks with this method of storage.

Thromboxane B_2 is a stable, inactive metabolite of the physiologically active but unstable TxA_2 , the half-life of which is 30 seconds at 37°C in aqueous solution [9]. We measured TxB_2 levels using a competitive binding radioimmunoassay. Anti-thromboxin B_2 antibody (rabbit), iodine 125-labeled TxB_2 tracer, TxB_2 standard, bovine serum albumin phosphate buffer, and magnetic goat anti-rabbit immunoglobulin G antibody were obtained from Advanced Magnetix Inc, Cambridge, MA. Assays were carried out according to the manufacturer's instructions. All results were expressed as picograms per milliliter.

We did not perform prostaglandin extraction from our samples, as falsely high levels have been reported after this procedure [10]. Cross-reactivity of anti- TxB_2 antibody with other prostaglandins is less than 1%. Thromboxane levels vary between individuals, as has been reported by other investigators [11, 12]. We used an external standard of plasma with known TxB_2 level for quality control.

Statistical Analysis

Values are expressed as mean $\pm$ standard error of the mean. In each group as a whole, differences in left atrial TxB_2 concentration compared with right atrial TxB_2 concentration were evaluated by two-way analysis of variance. Scheffé's multiple comparison test was applied to locate main sites of left atrial versus right atrial difference during CPB and reperfusion stages in both groups. Newman-Keul's multiple-sample comparison test was used to evaluate differences in TxB_2 levels compared with baseline in both the right atrium and the left atrium. Significance was determined at p less than 0.05.

Results

Total Cardiopulmonary Bypass Experiments

Figure 1 summarizes the results of the total bypass group. After introduction of cannulas in the right atrium and aorta, there was minimal change in left atrial and right atrial TxB_2 levels compared with baseline. With the onset

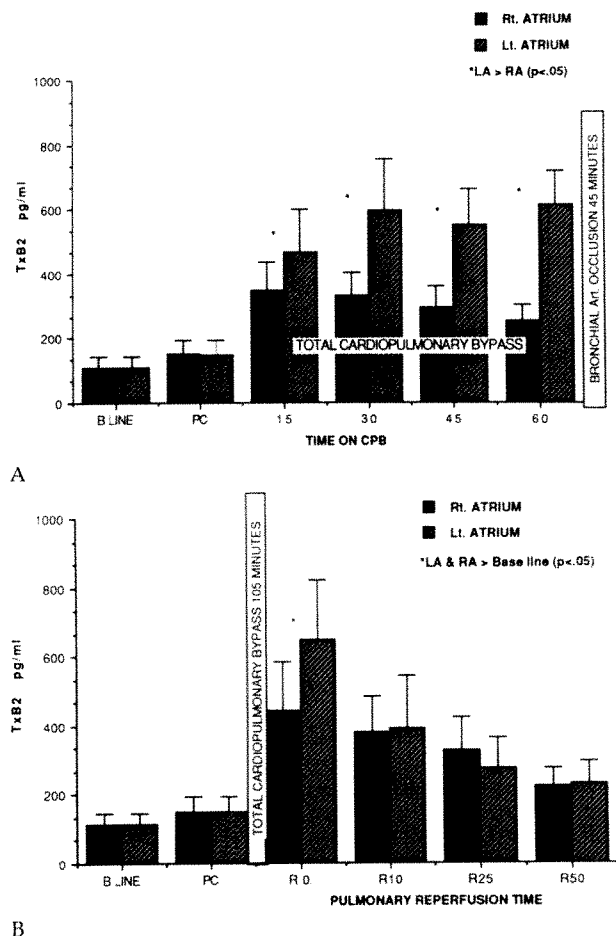


Fig 1. (A) Thromboxane B₂ (TxB₂) concentration in paired samples simultaneously drawn from the right atrium (RA) and left atrium (LA) before instrumentation (baseline [B LINE]), after cannulation of right atrium and aorta (postcannulation [PC]), and 15, 30, 45, and 60 minutes after the onset of total cardiopulmonary bypass (CPB) ($n = 7$). (B) Thromboxane B₂ concentration in paired samples simultaneously drawn from the right and left atria, before instrumentation, after cannulation of right atrium and aorta, and at intervals after reperfusion (R) of the pulmonary artery (at reperfusion = 0 minutes, then at 10, 25, and 50 minutes after termination of CPB). Time on total CPB = 105 minutes ($n = 7$).

of total CPB, there was a progressive increase (see Fig 1A) in TxB₂ levels in samples obtained from the left atrium (representing bronchial flow). There was also a slight, though not statistically significant, increase in right atrial TxB₂ levels, which was not sustained beyond the initial 15 minutes of CPB. Thus, an increasing gradient of TxB₂ levels between the left and right atria was documented during 60 minutes of CPB. Comparison between aortic cannula samples and those obtained simultaneously from the left and right atria at different intervals confirmed (Table 1) that TxB₂ levels at the aortic cannula site were similar to those in the right atrium (no increase across the bypass circuit) and significantly lower than left atrial levels ($p < 0.05$). The increase in left atrial TxB₂ concentration as compared with the right atrial concentration demonstrates an increase in TxB₂ level across the pulmo-

Table 1. Simultaneous Thromboxane Concentrations^a

Sample site	Thromboxane B ₂ (pg/mL)		
	Sample 1	Sample 2	Sample 3
Right atrium	287 ± 88	311 ± 89	243 ± 50
Aortic cannula	268 ± 68	260 ± 73	274 ± 76
Left atrium	537 ± 163	558 ± 178	570 ± 136

^a Thromboxane concentration in simultaneously drawn samples from the right atrium, aortic cannula, and left atrium at three predetermined intervals during cardiopulmonary bypass to establish whether a thromboxane concentration gradient might exist across the pump circuit (right atrium to aortic cannula) ($n = 7$). Values are shown as mean ± standard error of the mean.

nary circuit while only bronchial flow is present. During total bypass, before bronchoesophageal trunk occlusion, the mean left ventricular return was 1.08 ± 0.15 mL · min⁻¹ · kg body wt⁻¹, and for any given animal this flow remained constant during CPB. As some left ventricular thebesian return is included in this measurement, the actual bronchial flow would be slightly less than this mean value. Additionally, although more than 85% of the bronchial arterial supply in sheep is reportedly from the bronchoesophageal trunk, there is a right upper lobe bronchial artery that contributes the balance of bronchial flow [7]. In all of our animals there was a marked decrease in the left ventricular return after bronchoesophageal trunk occlusion.

At the onset of pulmonary reperfusion, after total CPB, significantly elevated levels of TxB₂ were immediately apparent in the left atrium and the right atrium compared with their respective control values. Subsequent samples taken 10, 25, and 50 minutes after reperfusion showed a rapid decrease in TxB₂ levels on both sides and abolition of the gradient between the atria (see Fig 1B).

Partial Cardiopulmonary Bypass Experiments

Figure 2 summarizes the results of the partial bypass group. The TxB₂ samples from this group were processed simultaneously in a batch subsequent to the samples from the total CPB group. The baseline values in this series of experiments were consistently higher than in the total CPB series, and comparisons are made only within the respective groups. With commencement of partial CPB there was an increase in TxB₂ level in both atria for the first 15 minutes, at which point right atrial TxB₂ values reached a plateau but the left atrial TxB₂ level continued to rise (see Fig 2A). After 45 minutes, however, there was a spontaneous decrease in TxB₂ levels. Only left atrial TxB₂ levels at 30 and 45 minutes showed a statistically significant increase compared with control, but there was no significant difference between left atrial and right atrial levels of TxB₂ at any time. Termination of partial CPB and complete reperfusion of lungs in this group did not significantly (see Fig 2B) affect TxB₂ levels on either side or the gradient between them.

Comment

Prostaglandins, including thromboxane, have a short half-life, and they are intercellular messengers [9]. These

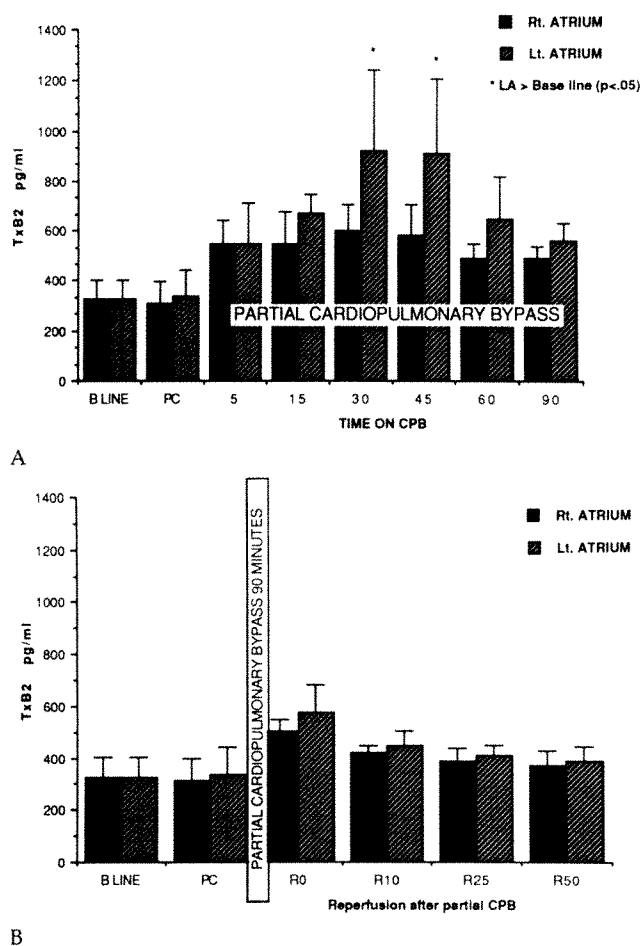


Fig 2. (A) Thromboxane B₂ (TxB₂) concentration in paired samples simultaneously drawn from the right atrium and left atrium (LA) before instrumentation (baseline [B LINE]), after cannulation of right atrium and aorta (postcannulation [PC]), and 15, 30, 45, 60, and 90 minutes after the onset of partial cardiopulmonary bypass (CPB) (n = 5). (B) Thromboxane B₂ concentration in paired samples simultaneously drawn from the right and left atria before instrumentation, after cannulation of right atrium and aorta, and at intervals after cessation of partial CPB (immediately after = 0, then at 10, 25, and 50 minutes). The total period of partial CPB = 90 minutes (n = 5). (R = pulmonary reperfusion.)

important mediators and modulators of inflammation are therefore most effective near the site of their production. If thromboxane plays a role in pulmonary pathophysiology, we would presume that it is synthesized in the lung and that the production would be stimulated by events associated with that pathophysiology. There is abundant evidence that different cell types in lung tissue possess the enzyme system necessary to synthesize thromboxane *in vitro* [5, 6]. Similarly, *in vivo* thromboxane generation by lungs in response to diverse stimuli has been documented in many clinical and experimental studies [13-18].

We hypothesized that thromboxane is produced in the lungs in association with the pulmonary ischemia of total CPB. Our results show an increasing difference in TxB₂ concentration between the left atrium and the right atrium with increasing time on total CPB (see Fig 1A). Because

right atrial TxB₂ levels were the same as aortic cannula levels during total bypass (see Table 1), there is no evidence for TxB₂ generation in the pump itself, and the right atrial concentrations can be considered to represent the TxB₂ concentration in bronchial arterial blood, which is the source of pulmonary tissue perfusion during CPB. With the termination of CPB and reperfusion of the pulmonary artery, high TxB₂ concentrations were observed in left atrial samples, but these rapidly decreased toward baseline (see Fig 1B). Thus, there is clear evidence of TxB₂ synthesis in the lung during total CPB, which continues only briefly or is "washed out" in the first few minutes of reperfusion. Although this study demonstrates that Tx generation occurs *in* the lung during total CPB, we cannot conclude that it is produced by the lung tissue itself. The specific cellular source that is stimulated may include sequestered platelets, white cells, or pulmonary endothelial cells.

To observe the effect of a similar period of extracorporeal circulation on systemic TxB₂ levels without concurrent pulmonary artery flow deprivation, we repeated a similar protocol in animals on partial CPB. We found that Tx generation in response to extracorporeal circulation alone (partial CPB) is self-limited, lasting 30 to 45 minutes (see Fig 2A), and its cessation is unrelated to any reperfusion phenomenon. This pattern is similar to the one observed by Peterson and associates [16] and Townsend and colleagues [11] in a veno-venous bypass model. The underlying mechanism of Tx generation in this situation may be systemic effects of extracorporeal circulation, for example, platelet activation and sequestration [2, 19, 20] or complement activation and polymorphonuclear leukocyte interaction [21]. The transient TxB₂ concentration elevation, with no significant left atrial to right atrial gradient, that occurs with partial CPB cannot entirely explain the TxB₂ concentration changes seen in the animals with total CPB.

The increased TxB₂ production associated with total CPB (see Fig 1A) and abolished by pulmonary reperfusion (see Fig 1B) suggests that the mechanism of this generation is related to blood flow through the lungs. It has been observed that tissue ischemia is a stimulus to Tx generation [3, 4]. Kobinina and associates [22] showed a linear relationship between cardiac anaerobiosis and Tx generation in their cardioplegia experiments. The basic stimulus to TxB₂ synthesis during ischemia may be hypoxia of the lung, or it may be directly related to reduced tissue perfusion.

Oxygen requirements of the lung are small (2% to 5% of total oxygen consumption [23]) but essential for its metabolic integrity [24]. Diversion of pulmonary blood from unventilated lungs leaves bronchial flow as the sole source of oxygen to the lungs. As bronchial flow is known to be inconstant [25, 26], there is a distinct possibility of hypoxia in pulmonary tissue during total CPB, with consequent pulmonary injury.

Ratliff and associates [27] observed that after CPB, pulmonary injury was related to lung tissue polymorphonuclear leukocyte infiltration and the duration of bypass. Chenworth and colleagues [28] also concluded that transpulmonary leukosequestration after CPB was related to aortic

cross-clamping time. The relationship between the duration of CPB, pulmonary polymorphonuclear infiltration, and subsequent pulmonary injury may be explained on the basis of generation of humoral mediators of inflammation by the ischemic lungs. Thromboxane increases in vitro polymorphonuclear diapedesis and chemotaxis [29], mediates diapedesis after ischemia through regulation of polymorphonuclear cells [30], and also causes ischemia-induced neutrophil activation, manifested by H_2O_2 production [31]. Thus, Tx is capable of mediating inflammatory reaction in the lungs. It remains to be established whether the increased concentration of Tx seen in these experiments might be pathophysiologic. Certainly, sporadic and unexplained noncardiac pulmonary edema may occur after operative procedures requiring CPB. The unexpected occurrence of such injury in previously healthy lungs raises the question of pulmonary parenchymal injury associated with CPB. The demonstration of Tx generation by the lung in association with total CPB may provide important insight into this phenomenon.

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Cavopulmonary Connection in Repair of Atrioventricular Septal Defect With Small Right Ventricle

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Between February 1991 and May 1992, 9 patients with a nonrestrictive inlet ventricular septal defect or complete atrioventricular septal defect and hypoplasia of the right ventricle underwent successful two-ventricle correction incorporating a bidirectional cavopulmonary anastomosis. Despite a satisfactory early postoperative course, large serous pleural effusions developed in 5 of them between 2 and 6 weeks after operation. Serial echocardiography showed an evolution of flow patterns in the superior vena cava from marked systolic reversal imme-

diately after operation to nearly continuous forward flow into both pulmonary arteries about 6 weeks later. This pattern was consistent with the transition from cardiac-dependent to respiratory-dependent caval flow. The development of pleural effusions appeared to coincide with the loss of systolic caval flow reversal and resolved after establishment of a predominantly respiratory-dependent flow pattern.

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Although more common when there is associated right ventricular outflow obstruction [1], hypoplasia of the right ventricle occurs infrequently in the presence of a complete atrioventricular (AV) septal defect with nonrestrictive interventricular communication [2]. Such patients are theoretically candidates for a Fontan type of operation [3] but often have associated incompetence of a common AV valve or suboptimal pulmonary vasculature for this procedure. The bidirectional cavopulmonary anastomosis (superior vena cava anastomosed end-to-side to the undivided pulmonary artery) has facilitated biventricular repair in patients with pulmonary atresia, intact ventricular septum, and hypoplasia of the right ventricle [4]. Herein, we describe the successful extension of this concept to 9 patients in whom the right ventricle was thought to be inadequate to support the pulmonary circulation after closure of a large interventricular communication.

Material and Methods

Patient Population

Nine patients ranging in age from 4 to 13 years (median age, 5.5 years) underwent repair of right ventricular outflow tract obstruction, closure of atrial and ventricular septal defects, and bidirectional cavopulmonary anastomosis between February 1991 and May 1992 (Table 1). Palliation had previously been accomplished in 4 patients with one or more systemic-pulmonary artery shunts, in 1

patient by balloon dilation of the right ventricular outflow tract [5], and in another patient by both balloon dilation and a systemic to pulmonary artery shunt. The primary diagnosis was complete AV septal defect combined with tetralogy of Fallot (4 patients), double-outlet right ventricle (2), pulmonary stenosis (1 patient), or extreme left ventricular dominance (1). The final patient, a boy aged 4.5 years, had a large inlet ventricular septal defect of the AV canal type, a secundum atrial septal defect, and infundibular and valvular pulmonary stenosis with bilateral superior venae cavae. Two children had a left superior vena cava draining to the left-sided atrium, and in 1 child, there was right atrial isomerism. Down's syndrome was present in 5 patients.

The cardiac malformation was investigated by preoperative echocardiography, cardiac catheterization, and angiography. All 8 patients with complete AV septal defect had mild or moderate left AV valve regurgitation, a finding based on the area and extension of the regurgitant jet into the left atrium using color Doppler ultrasound [6, 7]. Based on its angiographic appearance, the right ventricle was judged preoperatively to be moderately hypoplastic in 7 patients (Fig 1) [8]. In the remaining 2 patients, 1 of whom had double-outlet right ventricle, it was found to be severely hypertrophied with an inadequate cavity volume after insertion of the ventricular septal patch.

In all patients, the diameter of the right AV valve after repair as measured intraoperatively with Hegar's dilators was less than the mean normal value expected from the data of Rowlatt and associates [9] (Table 2). The preoperative right ventricular systolic pressure ranged from 30 to 120 mm Hg (median pressure, 74 mm Hg). The mean pulmonary artery pressure ranged from 10 to 20 mm Hg.

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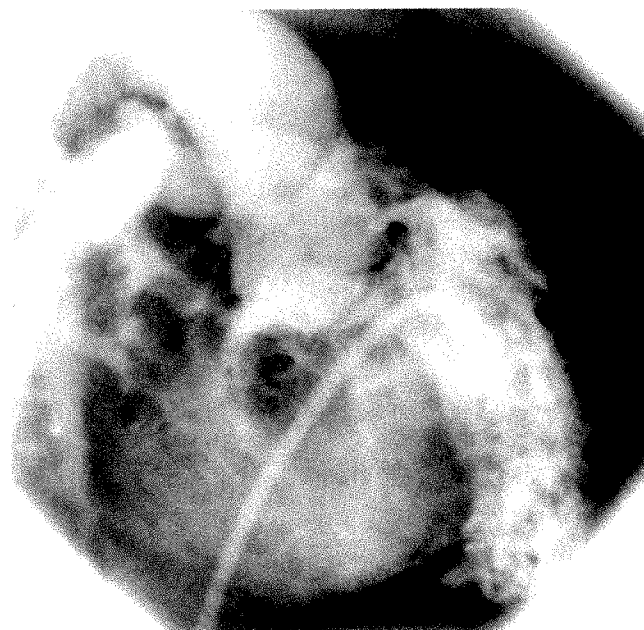
Address reprint requests to Dr McKay, Royal Liverpool Children's Hospital, Eaton Rd, Liverpool L12 2AP, England.

Table 1. Summary of Patient Data

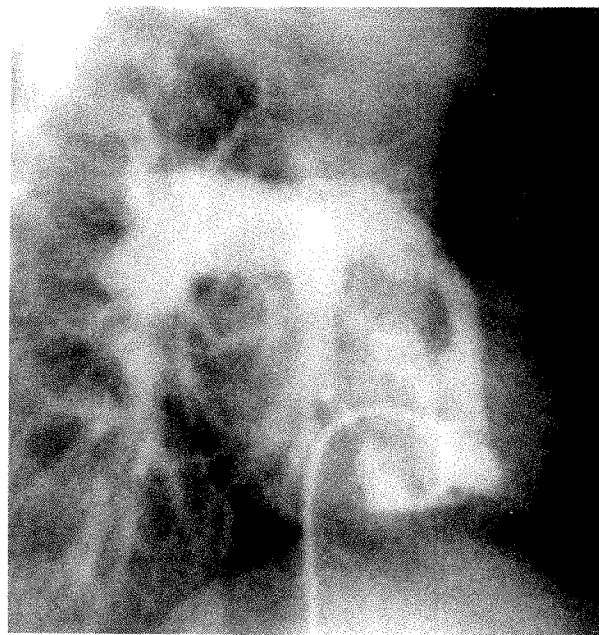
Patient No.	Sex	Previous Palliation	Age (y)	Diagnosis	Right Ventricle (Preop)	Mean PA Pressure (Preop) (mm Hg)	Follow-up (mo)	CVP (Postop) (mm Hg)	Pleural Effusion*
1	F	Right and left modified B-T shunt	13	Complete AVSD (type C); tetralogy of Fallot	Small and severely hypertrophied	15	16	12	None
2	M	None	5.5	Complete AVSD (type A) with extreme left ventricular dominance	Very small	20	15	15-18	Small left, postop week 3
3	F	Right modified B-T shunt	7.5	Complete AVSD (type C); tetralogy of Fallot	Small and severely hypertrophied	20	12	10-12	Large bilateral, postop week 3
4	M	None	4.5	VSD; secundum ASD; double-chambered RV; pulmonary stenosis	Very small; cavity virtually obliterated	10	13	15	Large left, postop week 5
5	M	Right classic B-T shunt	5	Complete AVSD (type C); tetralogy of Fallot	Half size of LV; severe hypertrophy	NE	11	18	Moderate left, postop week 6
6	F	Balloon dilation of pulmonary valve	7.2	Complete AVSD (type C); double-outlet RV; PDA	Good size; hypertrophied	20	10	20	Large right, postop week 2
7	M	None	5.6	Complete AVSD (type C); pulmonary stenosis; left SVC entering left atrium	Slightly small; hypertrophied	NE	(Residual VSD closed at 8 wk)	(8)	(None)
8	F	Right modified B-T shunt; balloon dilation of pulmonary valve	4.8	Complete AVSD (type C); tetralogy of Fallot	Very small; half size of LV; severe hypertrophy	NE	3	18	Large left, postop week 3
9	M	Left modified B-T shunt	4.0	Complete AVSD (type C); double-outlet RV; right atrial isomerism; left SVC entering pulmonary venous atrium	Very small	12	1	18	None

* Where applicable, the postoperative week indicates the onset of pleural effusion.

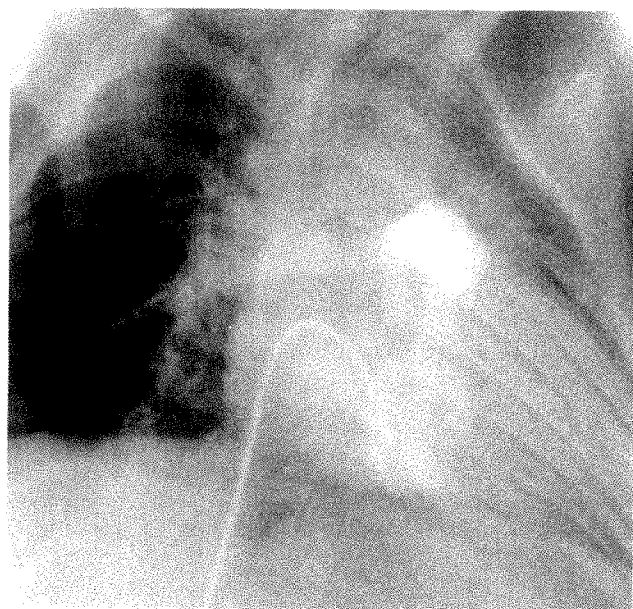
ASD = atrial septal defect; AVSD = atrioventricular septal defect; B-T = Blalock-Taussig; CVP = central venous pressure; LV = left ventricle; NE = not entered; PA = pulmonary artery; PDA = patent ductus arteriosus; RV = right ventricle; SVC = superior vena cava; VSD = ventricular septal defect.



A



B



C

Fig 1. Right ventricular angiograms demonstrating moderate hypoplasia of the right ventricle: (A) patient 2 (atrioventricular (AV) septal defect with extreme left ventricular dominance); (B) patient 3 (complete AV septal defect with tetralogy of Fallot); and (C) patient 4, (ventricular septal defect).

All preoperative anatomic findings were confirmed at the time of operation. Patients 1, 3, and 5 through 9 had a Rastelli type C AV septal defect, and patient 2 had a Rastelli type A common AV valve (see Table 1) [10].

Surgical Technique

Complete intracardiac repair was carried out through a midline sternotomy with moderate hypothermia (22°C) on cardiopulmonary bypass. Systemic to pulmonary shunts were controlled before the institution of perfusion, and the superior vena cava was cannulated near the innomi-

nate vein to facilitate a cavopulmonary connection. Atrioventricular septal defects were repaired using a two-patch technique with a comma-shaped extension of the Dacron patch to route the left ventricle to the dextroposed aorta [11, 12]. The interatrial communication was closed separately with a patch of autologous pericardium, with the coronary sinus left to drain into the right atrium. The left AV valve was repaired as needed to achieve competence.

Right ventricular outflow obstruction was relieved by a variety of methods including muscle resection, valvot-

Table 2. Surgical Techniques

Patient No.	RVOTO	ASD	VSD	RAVV ^a (mm)	CPA
1	Orthotopic PVR with homograft; PA reconstruction; muscle resection	Large; pericardial patch	Large; Dacron patch	17/27 (-10)	RSVC-RPA
2	None	Very large; pericardial patch	Moderate; Dacron patch	12/21 (-9)	RSVC-RPA
3	Pulmonary valvotomy; muscle resection	Very large; pericardial patch	Large; Dacron patch	16/22 (-6)	RSVC-RPA
4	Pulmonary valvotomy; muscle resection	Large ASD 2; pericardial patch	Large, confluent; Dacron patch	20/22 (-2)	RSVC-RPA; LSVC-LPA
5	Orthotopic PVR with homograft; muscle resection	Very large; pericardial patch	Large; Dacron patch	15/20 (-5)	RSVC-RPA
6	Orthotopic PVR with aortic homograft; muscle resection	Very large; pericardial patch	Large; Dacron patch	15/22 (-7)	RSVC-RPA
7	Pulmonary valvotomy; muscle resection; PA reconstruction	Very large; pericardial patch	Large; Dacron patch	18/20 (-2)	LSVC-LPA
8	Orthotopic PVR with homograft; muscle resection; PA reconstruction	Very large; pericardial patch	Large; Dacron patch	16/20 (-4)	RSVC-RPA
9	Orthotopic PVR with homograft; muscle resection	Very large; pericardial patch	Moderate; Dacron patch	18/22 (-4)	LSVC-LPA; RSVC ligated

^a Data are shown as observed/expected; numbers in parentheses are the standard deviations below mean normal.

ASD = atrial septal defect; ASD 2 = secundum atrial septal defect; CPA = cavopulmonary anastomosis; LPA = left pulmonary artery; LSVC = left superior vena cava; PA = pulmonary artery; PVR = pulmonary valve replacement; RAVV = right atrioventricular valve; RPA = right pulmonary artery; RSVC = right superior vena cava; RVOTO = right ventricular outflow tract obstruction; VSD = ventricular septal defect.

omy, and division of the pulmonary annulus (see Table 2). When this resulted in loss of a competent valvular mechanism, a complete homograft was implanted in the orthotopic position, using the attached branch pulmonary arteries as an onlay patch to relieve bifurcation stenoses as needed [13]. Finally, during rewarming, the cavopulmonary anastomosis was constructed with continuous 7-0 polydioxanone monofilament suture (Ethicon). This was done at the site of any previous aortopulmonary shunt after resection of the Gore-Tex conduit or subclavian artery, or to the upper surface of the pulmonary artery. The azygos or hemiazygos vein, if not previously divided, was ligated.

Results

Five patients had an uncomplicated early postoperative course and were extubated within 48 hours after operation. Four remained ventilator dependent for 7 to 10 days, 3 because of pulmonary infection and 1 because of an intracardiac shunt. The latter patient underwent closure of a residual ventricular septal defect 8 weeks after the original operation and recovered without further complications. An electrocardiogram made at discharge showed normal sinus rhythm in each patient. Medications at

discharge were digoxin, furosemide, and amiloride hydrochloride in standard therapeutic doses.

Large serous pleural effusions developed between 2 and 6 weeks after operation in 5 patients, including the patient with a residual ventricular septal defect. The effusions were bilateral in 1 patient, predominantly left sided in 3, and predominantly right sided in 1. Temporary intercostal drainage was necessary in 4 patients, and all effusions resolved after 4 weeks or less of conservative management.

Follow-up

All patients have been followed up by regular clinical examination and two-dimensional Doppler (pulsed-wave, continuous-wave, and color-flow imaging) echocardiography. The median duration of follow-up is 11 months (range, 1 to 16 months).

Echocardiography

M-mode, two-dimensional, and Doppler echocardiography were performed after operation and at hospital discharge in all patients. In addition, serial follow-up echocardiographic studies were also performed. M-mode echocardiograms of the left ventricle confirmed that the left ventricular ejection fraction was normal for age in all

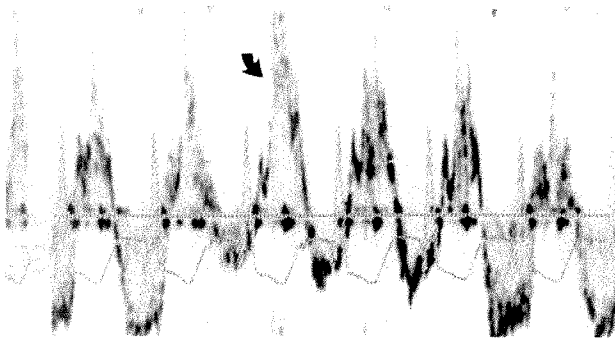


Fig 2. Pulsed Doppler echocardiographic recording from the superior vena cava 2 days after operation. There is a marked high-velocity flow reversal corresponding to ventricular systole (arrow).

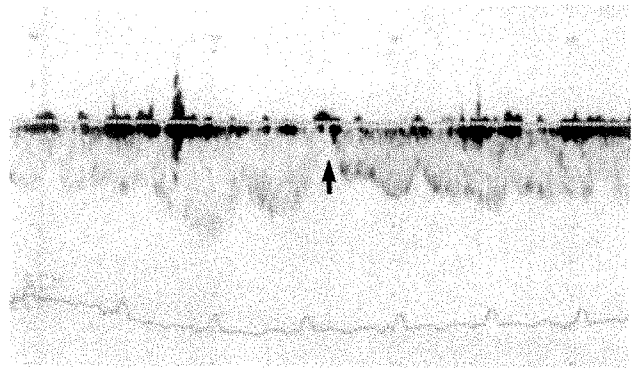


Fig 4. Pulsed Doppler recording of superior vena caval flow 1 month after operation. There is nearly continuous forward flow to the lung, with a brief cessation in flow (arrow) corresponding to peak expiration.

patients. At the time of hospital discharge, 1 patient had a small residual shunt at the ventricular level with a high velocity of transeptal flow on continuous-wave Doppler examination, suggesting a low right ventricular systolic pressure [14]. All 8 patients who had repair of an AV septal defect showed a mild degree of left AV valve regurgitation on Doppler color-flow imaging. None of the patients had evidence of major residual right ventricular outflow tract obstruction. Detailed pulsed Doppler examination of the flow patterns within the superior vena cava, right AV valve, and main and branch pulmonary arteries was performed using a combination of parasternal and suprasternal scan positions.

Four distinct patterns of flow in the superior vena cava were demonstrated, depending largely on the interval from operation. In the immediate postoperative period, there was a marked reversal of flow corresponding to ventricular systole (Fig 2). This systolic reversed flow often exceeded diastolic forward flow into the pulmonary artery both in peak velocity and duration. Approximately 2 weeks after operation, the systolic flow reversal became less marked and occurred only in early systole (Fig 3). In

2 patients, the systolic flow reversal was no longer present 6 weeks later. Instead there was a complete cessation of flow within the superior vena cava immediately after ventricular systole in 1, and in the other, low-velocity forward flow into the pulmonary artery was observed occurring throughout the cardiac cycle, with a brief cessation of flow at peak expiration (Fig 4).

In all patients, the right AV valve inflow pattern was abnormal initially, with the late filling peak ("A" peak, corresponding to atrial systole) being of higher velocity than the early ("E") filling peak. This pattern was not evident in 6 of the 9 patients at the most recent follow-up. In these 6, the velocity of the early filling peak had become equal to or exceeded that of the late peak.

In the early postoperative period (up to 2 weeks after operation), interrogation of flow patterns in the main pulmonary artery just distal to the pulmonary valve showed atrial augmentation of pulmonary flow [15], with early filling of the main pulmonary artery corresponding to atrial systole (Fig 5). This phenomenon also had disappeared within 6 to 8 weeks after repair in all patients.

Initially, the right pulmonary artery distal to the cavo-

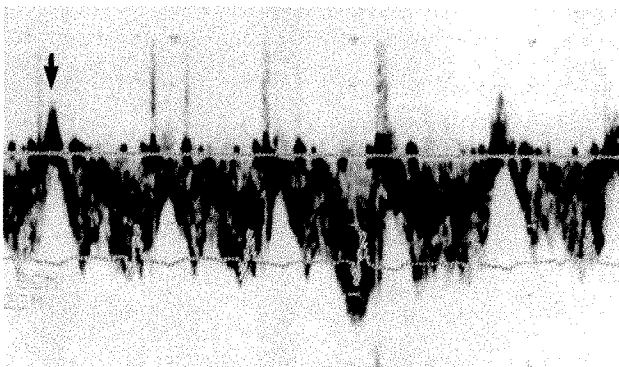


Fig 3. Pulsed Doppler recording from the superior vena cava 2 weeks after operation. Systolic flow reversal (arrow) is markedly less prominent and of shorter duration.

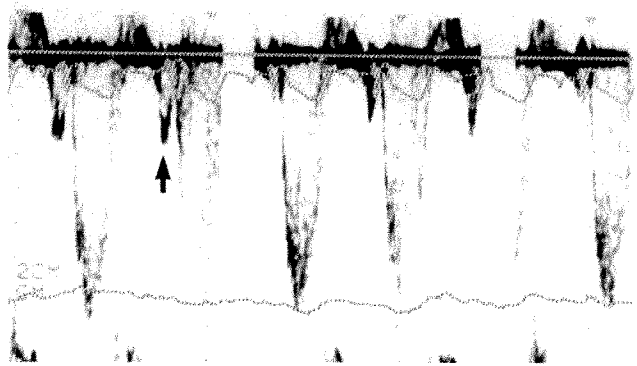


Fig 5. Pulsed Doppler recording in the main pulmonary artery, just distal to the pulmonary valve, 1 week after repair. There is a biphasic pattern of flow, with the earlier peak (arrow) corresponding to atrial systole.

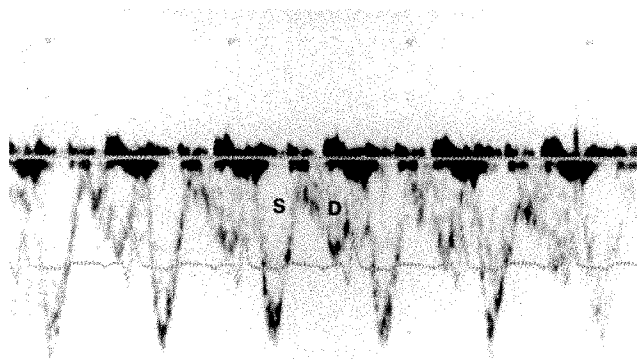


Fig 6. Pulsed Doppler recording in the distal right pulmonary artery 2 weeks after repair. There is a high-velocity peak corresponding to ventricular systole (S), and a lower-velocity diastolic flow (D) from the superior vena cava. In contrast, the left pulmonary artery demonstrated only systolic flow.

pulmonary connection demonstrated a biphasic pattern of flow, with a higher-velocity peak corresponding to ventricular systole and a lower-velocity diastolic flow from the superior vena cava (Fig 6). In contrast, the main pulmonary artery, left pulmonary artery, and right pulmonary artery proximal to the cavopulmonary connection showed a monophasic systolic flow peak. At the most recent follow-up, a diastolic contribution to flow from the superior vena cava was evident in both the right and left pulmonary arteries in all patients. These various flow patterns are summarized in Table 3.

Comment

Although less obvious than hypoplasia of the left ventricle, there are several situations in which the right ventricle may be inadequate to convey the entire cardiac output to the pulmonary circulation after closure of a large inter-ventricular communication. In complete AV septal defect with tetralogy of Fallot, about 42% of postmortem specimens have been found to have anatomically smaller than normal right ventricles [1]. This was true of all 6 patients with Fallot's tetralogy or pulmonary stenosis in this series. In addition to a morphologically small chamber, the ventricle can be functionally restrictive as the result of

muscle hypertrophy and reduced compliance, which may be further exacerbated by cardiopulmonary bypass. Such factors generally improve after relief of outflow obstruction but still contribute important limitations to right ventricular performance in the early postoperative period. A ventricle that might otherwise have been adequate also may become compromised by the position of the patch inserted for closure of the ventricular septal defect. In both of our patients with double-outlet right ventricle, the Dacron extension connecting the left ventricle to the aorta occupied a substantial portion of the right ventricular chamber.

Although good results have been achieved with surgical correction of the balanced forms of complete AV septal defect with tetralogy of Fallot [3, 12] or other associated anomalies [11], patients with severe ventricular dominance continue to have a high early and late mortality [2]. In our experience, this outcome usually becomes manifest a few days after operation as progressive right ventricular failure leading to multiorgan dysfunction. Even though a competent pulmonary valve is ensured by implantation of an orthotopic pulmonary homograft, 10% to 15% of such patients eventually die of sepsis, fluid retention, or renal failure.

The Fontan operation is an option for patients with extreme left ventricular dominance [3], but clinical and experimental studies [8, 16] of other malformations have demonstrated improved functional results when the hypoplastic right ventricle is incorporated into the subpulmonary circulation. In tricuspid atresia, this has resulted in a lower right atrial pressure and improved left ventricular ejection fraction [17]. Cardiac output is thought to be enhanced by improved left ventricular filling and augmentation of left ventricular systolic function [18, 19]. Although the volume of right ventricle needed to contribute positive stroke work is uncertain, some data suggest that this should be approximately 30% of normal [16, 20]. Thus in patient 2, in preference to ventricular exclusion or total cavopulmonary connection, the hemodynamic contribution of the small right ventricle (see Fig 1A) was conserved by repair of the AV septal defect.

The minimum right ventricular size that is necessary to accommodate the entire systemic venous return is less well characterized. Two classifications of ventricular size

Table 3. Summary of Evolution of Flow Patterns by Doppler Echocardiography

Time of Pattern	SVC Flow	Pulmonary Flow	RAVV Flow
Immediately postop	Prominent systolic reversal	Atrial augmentation in MPA; biphasic flow in distal RPA only	"A" peak greater than "E" peak (poor RV compliance)
2 weeks postop	Less marked systolic reversal	...	...
6 to 8 weeks postop	No reversal, but complete cessation in systole	...	...
Most recent	Nearly continuous forward flow with brief cessation at end-expiration (respiratory dependent)	Continuous systolic and diastolic flow in RPA and LPA	"E" peak equal to or greater than "A" peak (improved RV compliance)

"A" peak = late filling peak corresponding to atrial systole; "E" peak = early filling peak; LPA = left pulmonary artery; MPA = main pulmonary artery; RAVV = right atrioventricular valve; RPA = right pulmonary artery; RV = right ventricular; SVC = superior vena cava.

based on the tripartite approach to right ventricular morphology have evolved from experience in patients with pulmonary atresia and intact ventricular septum, and are now widely used in surgical decision-making [8, 21, 22]. Both endeavor to predict the utility of incorporating a small right ventricle into the final repair and use the tricuspid valve diameter as an indirect index of right ventricular cavity size. Applying either classification to patients in this series, we found that all hearts had postrepair right AV valve diameters that were at least two standard deviations below the mean normal expected value for body surface area (see Table 2), and all had subjectively moderate to severe hypoplasia of the right ventricle. Consequently, when these findings were confirmed at the conclusion of the intracardiac repair, a bidirectional cavopulmonary anastomosis was performed to reduce the volume load on the right ventricle. In the only patient with a nearly adequate right ventricle and a borderline right AV valve ($z = -2$) (patient 7), a further incentive to use the cavopulmonary connection was the presence of a left superior vena cava draining to the left atrium.

Although only 1 patient has undergone cardiac catheterization postoperatively, echocardiography demonstrated several interesting and important hemodynamic details. Right ventricular compliance immediately after operation was clearly impaired as evidenced by an abnormal pattern of right AV valve inflow, with ventricular filling dependent to a greater degree on atrial systole and with an atrial contribution to pulmonary flow. The right ventricle, however, was capable of useful pump function from the outset, and Doppler recording of pulmonary artery flow showed a dominant systolic filling peak. The atrial contribution to pulmonary flow disappeared within 4 to 6 weeks postoperatively without any apparent change in right ventricular size, again suggesting improved right ventricular compliance with time, enabling the ventricle to better accommodate systemic venous return from the inferior vena cava.

We are not aware of any previous characterization of flow patterns in the superior vena cava or pulmonary arteries after a bidirectional cavopulmonary anastomosis in which the right ventricle also contributes to filling of the pulmonary arteries through the pulmonary valve [23]. In the majority of reported series, either antegrade blood flow through the pulmonary valve is minor or the proximal pulmonary artery has been divided as part of the procedure. As expected, a high degree of venous distensibility enabled the superior vena cava to rapidly accommodate systolic flow from the right ventricle in the immediate postoperative period. With time, there probably was an improvement in compliance of the pulmonary-vascular bed and left ventricle. Thus, with increasing interval from operation, there occurred a marked decrease in the duration and peak velocity of systolic reversed flow in the vena cava and eventually nearly continuous forward flow into the pulmonary artery. This confirms that the previously demonstrated respiratory dependence of pulmonary blood flow after the total cavopulmonary connection [24, 25] may still be operative in these patients, despite the

right ventricular contribution of pulsatile flow during ventricular systole. Perfusion studies have demonstrated that the bidirectional cavopulmonary anastomosis in isolation favors superior vena caval blood flow into the right lung [23]. When there is added forward flow into the pulmonary arteries from the right ventricle, there initially appears to be no contribution at all from the cavopulmonary anastomosis to the perfusion of the left lung, as shown by a complete absence of diastolic flow in the left pulmonary artery. However, continuous diastolic flow to both lungs eventually developed in all patients.

Although the etiology of serous effusions after a Fontan procedure remains obscure, the pathogenesis of late-onset pleural drainage among the patients in this series probably reflects an even more complex interaction of physiological variables. Pulsatile blood flow is known to facilitate movement of interstitial fluid and lymph [26], and formation of pleural fluid may depend, in part, on the systemic venous pressure (to which the parietal pleura and thoracic duct drain) and pulmonary venous pressure (which receives the visceral pleural drainage). Plasma atrial natriuretic peptide has also been implicated in the formation of pleural effusions after total cavopulmonary connection [27]. It is possibly some imbalance of these homeostatic mechanisms during ventricular recovery and the hemodynamic evolution of the pulmonary circulation that lead to the formation of pleural effusions in some of these patients.

In conclusion, the combination of intracardiac repair of a large ventricular septal defect with concomitant bidirectional cavopulmonary anastomosis retains the advantages of a functional ventricle in the subpulmonary circulation and simultaneously reduces volume overload of a hypoplastic right ventricle. In patients with small or hypertrophied right ventricles for whom higher than normal right ventricular pressures and diminished compliance can be expected, these factors may prevent the onset of insidious right ventricular failure in the early postoperative period. However, as ventricular function improves, and for reasons that are not clear, there is a high likelihood of transient pleural effusions developing. The long-term consequences of this unusual pulmonary circulation, particularly in regard to the development of arteriovenous malformations, are also unknown.

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Biomechanical Study of Sternal Closure Techniques

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Median sternotomy is the most commonly used incision in cardiothoracic surgery. Closure of this incision is usually performed with parasternal wires, but alternate techniques have been proposed to improve closure stability. This study compares biomechanical stability of standard wire (No. 5 stainless steel) with that of three types of band closure: 5-mm Mersilene ribbon, 5-mm stainless steel band, and 5-mm plastic band. Eight bisected cadaver sterna were reapproximated using each method of sternal fixation and tested for biomechanical stability using an MTS Bionix 858 Biomechanical Tester. Loads of 50, 100, 150, and 200 Newtons (1 Newton = 1 kg · m/s²) were applied as a distracting force across the closure. A linear regression line of displacement as a function of increasing load was determined for each closure method; the slope of this line is inversely proportional to fixation stability. Displacement and load

correlated linearly for each closure ($r = 0.99$). Mean slopes were 0.012 mm/Newton (95% confidence limits, 0.0098 to 0.0142 mm/Newton) for No. 5 stainless steel wire, 0.014 mm/Newton (95% confidence limits, 0.0118 to 0.0162 mm/Newton) for plastic band, 0.017 mm/Newton (95% confidence limits, 0.0148 to 0.0192 mm/Newton) for Mersilene ribbon, and 0.017 mm/Newton (95% confidence limits, 0.0148 to 0.0192 mm/Newton) for 5-mm steel band. No. 5 stainless steel wire provided the most stable closure, although statistical significance was achieved only in comparison with Mersilene ribbon and stainless steel band ($p < 0.05$). The superior stability of stainless steel wire closure may be due to tightening of the wires by twisting, which results in more tension across the reapproximated sternal halves than with other methods.

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The median sternotomy, first popularized by Julian and co-workers in 1957 [1], has become the most commonly used incision in cardiothoracic surgery. Although closure of this incision is usually simple and straightforward, healing complications such as instability, non-union, and infection still occur in 0.4% to 5% of cardiac surgical patients [2-8]. Furthermore, widespread use of the internal mammary artery graft for coronary revascularization and the growing proportion of reoperative procedures have contributed to further increases in the incidence of sternal complications [3] and have raised interest in the optimal method of sternal closure.

Closure of the median sternotomy incision is usually performed with parasternal wires, but alternate techniques have been devised to improve closure stability. These alternate techniques attempt to redistribute tension across the incision by banding or by complex wiring techniques [9-20]. However, few studies have attempted to quantitate the degree of fixation achieved by these different approaches.

In orthopedic surgery, different methods of bony fixation have been compared in various models by measuring displacement of the bony structures when subjected to increasing load. The slope of displacement over load is "stiffness" and is a measure of fixation stability. A stiffer

repair has less displacement at each load and is more stable. Typically, a biomechanical tester is used to apply increasing load to a repair; displacement is measured with a strain gauge. Employing a biomechanical tester, we compared the stability of simple No. 5 stainless steel wire closure with that of 5-mm Mersilene ribbon (woven polyester suture; Ethicon Laboratories, Somerville, NJ), 5-mm plastic band (Panduit Corporation, New Lenox, IL), and 5-mm steel band closure (Panduit Corporation) (Fig 1).

Material and Methods

Study Protocol

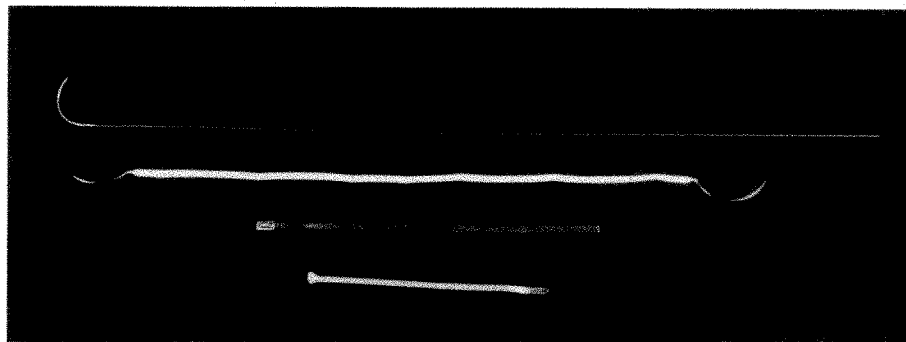
Eight cadaver sterna were removed en bloc with approximately 10 cm of rib length on each side of ribs two through six. Median sternotomies were performed with an oscillating saw. Each sternum was prepared for mechanical testing in the following manner: Steinman pins were drilled through each rib and the ribs then potted in a rectangular steel mold filled with adhesive (Fig 2). The mold was designed for the jig of an MTS Bionix 858 Universal Biomechanical Tester. An initial loading test was performed on one sternum fixed with No. 5 stainless steel wire. The sternum was tested in tension, with the load applied as a distracting force across the closure at a rate of 1.25 mm/s until failure. The recorded load to failure was 650 Newtons (1 Newton = 1 kg · m/s²). Subsequent testing was performed at loads well below this failure load to stay within the elastic range of the specimen.

Four methods of sternal fixation were studied: No. 5

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Fig 1. Materials used in sternal closure (top to bottom) No. 5 stainless steel wire, 5-mm Mersilene ribbon, 5-mm steel band, and 5-mm plastic band.



stainless steel wire, 5-mm plastic band, 5-mm Mersilene ribbon, and 5-mm steel band. Each was tested in random sequence on every sternum. Testing consisted of repetitive loading for 100 three-second cycles with four different loads: 50, 100, 150, and 200 Newtons. The average displacement, as measured by a strain gauge between cycles 10 to 100, was the displacement for that particular load.

The four methods of closure were compared based on the change in displacement with increasing loads. Regression analysis yielded a least-squares estimate of slope of displacement versus load. Repeated-measures analysis of variance was performed to compare the slopes of displacement versus load for each method. Mean and 95% confidence limits (CL) of slope for each method were

calculated and plotted. Methods were considered to be significantly different at p less than 0.05 if the 95% CL did not overlap.

Surgical Technique

Mersilene ribbon is a woven polyester tape 5 mm wide and 30 cm long, swedged on two large blunt needles. It is placed around the lateral border of the sternal body in the intercostal space. A half-knot is placed and the tape is tightened with a clamp placed across the half-knot to avoid slippage before the second knot. Two additional square knots are then placed. The No. 5 stainless steel wire was passed around the sternal body in the intercostal space and tightened with symmetric twisting using a large needle driver. The plastic and steel bands were passed around the sternal body in the intercostal space with a curved clamp, and then threaded through the buckle and secured with an applicator gun.

Results

There was a strong linear correlation between displacement and load for each method tested ($r = 0.99$). The slope of displacement versus load was 0.012 mm/Newton (95% CL, 0.0098 to 0.0142 mm/Newton) for No. 5 stainless steel wire, 0.014 mm/Newton (95% CL, 0.0118 to 0.0162 mm/Newton) for 5-mm plastic band, 0.017 mm/Newton (95% CL, 0.0148 to 0.0192 mm/Newton) for Mersilene ribbon, and 0.017 mm/Newton (95% CL, 0.0148 to 0.0192 mm/Newton) for 5-mm steel band. Pairwise comparisons showed No. 5 stainless steel wire a more stable closure than Mersilene ribbon and steel band ($p < 0.05$), but not statistically better than plastic band. There were no significant differences among plastic band and Mersilene ribbon or steel band.

Comment

Sternal nonhealing and sternal infection are serious complications of median sternotomy and lead to considerable morbidity and mortality [3-5]. Mechanical instability of the closure is an important factor contributing to both nonhealing and infection. Previous studies have documented that prolonged cardiopulmonary bypass, excessive postoperative bleeding, depressed cardiac output, reexploration for hemorrhage, and use of the internal mammary artery graft also predispose to healing compli-

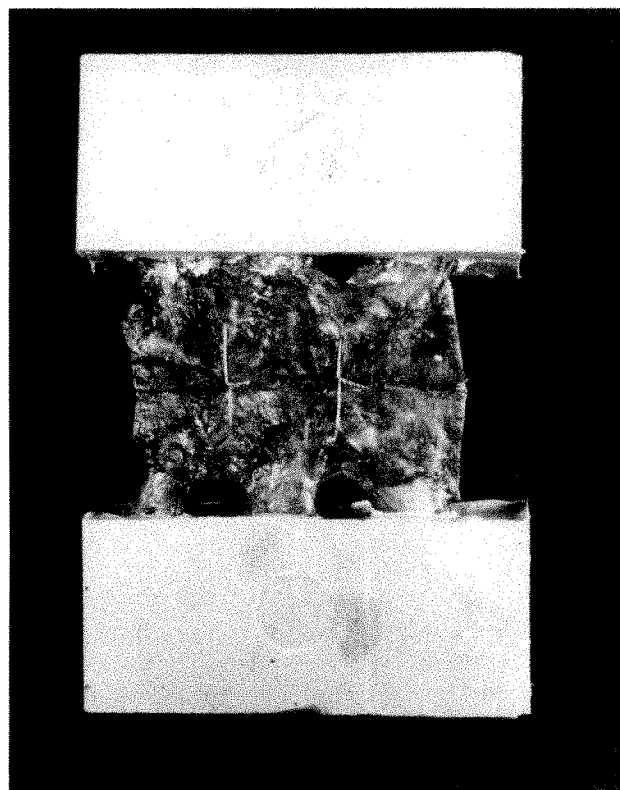


Fig 2. Sample sternum secured in mold for testing in MTS Biomechanical tester. Depicted sternum has been closed with No. 5 stainless steel wire.

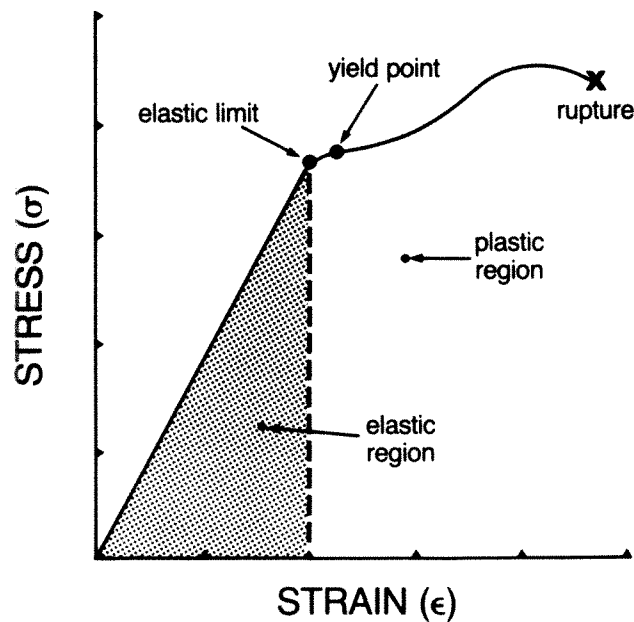


Fig 3. Relationship of stress and strain.

cations [2-8], but inadequate mechanical stabilization of the sternum is undoubtedly an important variable, although difficult to identify and quantitate. Because of the high morbidity and mortality attending sternal complications, there is interest in alternate methods of sternal fixation [9-20].

There are theoretic advantages of banding techniques over wire closure for sternal fixation. By spreading load over a larger surface area, the applied stress (force/area) is less. A band repair may exhibit less displacement with a given load and be stiffer. Moreover, at equivalent loads, a band should be less likely to break or cut into the sternum. Therefore, we chose to compare standard wire closure with three types of band closure: 5-mm Mersilene ribbon tape, 5-mm plastic band, and 5-mm stainless steel band.

Because of the unique shape of the human sternum, use of cadaver specimens is the best model to assess sternal closure stability. The configuration that a band or wire assumes around the sternum influences the way in which tension is applied to the sternum and thus affects stability. Moreover, due to the wide variability in stiffness among sterna, each fixation technique must be randomly tested on each specimen.

Each cadaver specimen subjected to tensile loading has a characteristic stress-strain curve (Fig 3). On the stress-strain curve, the initial straight line represents elastic behavior. Elastic behavior is characterized by full recovery from deformation, ie, a force will deform the material, but on removal of the force the material will regain its original dimensions. There is a linear relation between force and deformation, with each unit of force producing the same increment in deformation. The yield point is the point on the curve where an increase in strain or deformation occurs without significant increase in stress or load. Beyond the yield point, the material deforms with plastic

behavior; any strain developed along this portion of the curve results in permanent change of the material. To stay within the elastic range of the specimen it is important to stay well below the yield point.

Initial tensile loading tests indicated a yield point of about 650 Newtons for a representative human sternum. Therefore we elected to use 50-Newton increments between 50 and 200 Newtons. One hundred 3-second cycles were applied for each test to mimic movement associated with ventilation. Average displacement was compared with load from cycles 10 to 100.

In this model of sternal fixation, using a biomechanical tester to compare repair stability, we were unable to document an advantage of a band-type repair over standard steel wire closure. In fact, under these conditions, No. 5 stainless steel wire proved superior to steel band and Mersilene ribbon. At loads within the elastic range of sternal deformation, stainless steel wire fixation resulted in less sternal motion than either Mersilene ribbon or steel band. The advantages of steel wire fixation over Mersilene ribbon appear to be due to the fact that steel is stiffer than Mersilene and the symmetric twist closure is superior to knot fixation in maintaining tension across the sternal halves. A consistent, reproducible amount of tension can be applied and maintained in cerclage wiring by twist fixation [21, 22]. In contrast, during tying, tension must be released for the second half-knot to be tied. The advantage of steel wire over steel band may also result from its superior ability to conform to the shape of the sternum. Steel band was designed to fit circular objects such as pipes, but its prominent buckle hinders a secure fit around the sternum.

When compared with plastic band closure, steel wire closure was more stable, although this difference did not reach statistical significance because of the limited number of specimens. The plastic band conforms better to the sternum because of its less prominent buckle and superior malleability.

As is commonly accepted in orthopedic surgery, we assume that more stable bony fixation leads to better healing in sternal closure. Undoubtedly, other factors such as bacterial contamination, sternal ischemia, diabetes, and unusual disrupting forces (violent coughing) also contribute to healing problems, but many of these are beyond the control of the cardiothoracic surgeon. Therefore, additional efforts to improve stabilization in the face of these risk factors is essential.

Encouraged by these experimental results, we continue to use stainless steel wire closure at The Johns Hopkins Hospital despite experience with other methods of closure. In our current practice, we place one or two No. 6 stainless steel wires in the manubrium, followed by "figure-of-8" wires around the sternum between the costal cartilages. We have not compared figure-of-8 closure with simple interrupted sutures in this study, but we believe that figure-of-8 wiring maintains the benefits of cerclage wiring and still allows the force to be displaced over a greater surface area, recruiting the theoretic benefits of banding.

We conclude that standard stainless steel wire closure is

more stable than Mersilene ribbon and steel band when the applied load is within the elastic range of the human sternum. Although a band theoretically should allow less plastic deformation than wire, this advantage is lost if the band cannot maintain tension between the sternal halves because of poor fit. Wire closure remains the standard against which alternate fixation methods should be compared. Finally, this study suggests that new methods of sternal fixation can be evaluated in vitro with biomechanical testing methods before clinical use.

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Pulmonary Artery Balloon Counterpulsation: Safe After Peripheral Placement

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Pulmonary artery balloon counterpulsation is a promising experimental technique for treatment of right ventricular failure. However, clinical application has been limited in that the only device presently available (the large-volume intraaortic balloon) must be placed within a synthetic graft. Because a balloon with a smaller volume (which could be placed through a peripheral vein and be contained entirely within the pulmonary artery) would make the technique feasible on a wider scale, we tested an 8-mL pulmonary artery balloon placed through the femoral vein in 12 dogs. Two groups of animals were compared. One group had the pulmonary artery balloon in place but not counterpulsating; the other had the pulmonary artery balloon in place and counterpulsating. Each group was studied for 12 hours. A variety of hemodynamic parameters were measured. Effective dia-

stolic augmentation and systolic unloading were noted in all 6 dogs that underwent counterpulsation (5.0 ± 1.1 mm Hg of diastolic augmentation and 9.5 ± 1.6 mm Hg of systolic unloading). Pulmonary function, as measured by arterial blood gas sampling and pulmonary vascular resistance, was not impaired. Examination of the heart and lungs showed no detrimental pathologic effects of pulmonary artery balloon counterpulsation. Placement of the balloon through a peripheral vein with a guidewire was easy and uncomplicated. We conclude that pulmonary artery balloon counterpulsation is safe over an extended period of 12 hours in the canine model and that diastolic augmentation and systolic unloading can be produced.

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Pulmonary artery balloon counterpulsation (PABC) is a promising technique for treatment of right ventricular failure. The technique has produced dramatic improvement in sporadic clinical cases of right ventricular failure [1-3]. In such cases, a standard intraaortic balloon pump has been inserted into a synthetic vascular graft anastomosed in an end-to-side fashion to the pulmonary artery; complete recovery from right ventricular failure has been reported. Animal studies have also shown PABC to ameliorate experimentally induced right ventricular failure over the short term (ie, less than 1 hour) [4-6]. However, the requirement for sternotomy has limited clinical applicability of PABC.

We developed a device that could be inserted percutaneously through the femoral vein and was small enough to fit entirely within the pulmonary artery. We then tested its hemodynamic efficacy and safety over an extended period of 12 hours.

Material and Methods

Adult mongrel dogs weighing 20 to 30 kg were fully anesthetized using pentobarbital (20 mg/kg) and halo-

thane (0.5% to 1.5%). A volume ventilator (Harvard Apparatus Company, Inc, Millis, MA) was used to administer both inhalational anesthetic agents and oxygen. Lactated Ringer's solution or normal saline solution was administered intravenously to maintain a urine output of 0.5 to $1.0 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and a central venous pressure of 1 to 5 mm Hg.

The pulmonary artery balloon device inserted was manufactured by Datascope, Inc (Oakland, NJ). It had an 8-mL capacity, a 16-mm proximal diameter (tapering gradually to its distal insertion on a 9.5F catheter), and a length of 55 mm. This device provided the most appropriate dimensions in our canine model. (Other devices with volumes of 10.5 and 20 mL and proximal diameters of 17 and 19 mm, respectively, required excessive amounts of pressure to fill completely in preliminary trials.)

Animals were divided randomly into two groups. The first group consisted of 6 control animals. In these animals, an arterial cannula was placed in the right femoral artery for blood pressure monitoring and arterial blood gas sampling. The right femoral vein was used for both central venous pressure monitoring and volume infusion. The right external jugular vein was isolated, and a pulmonary artery catheter (American Edwards Laboratories, Irvine, CA) was passed into the pulmonary artery. This catheter was used to monitor pulmonary artery pressures,

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pulmonary capillary wedge pressure, and cardiac output (by the thermodilution technique). The left femoral vein was exposed for subsequent introduction of the PABC device. A right anterolateral thoracotomy was performed through the fourth intercostal space. After the pericardium was opened, a catheter was inserted through the anterior wall of the right ventricle into the right ventricular cavity for measurement of right ventricular pressures and the positive and negative first derivative of right ventricular pressure (RV dP/dt). After insertion of a 28-gauge chest tube through a separate stab wound incision, the thoracotomy was closed. A suprapubic cystostomy allowed hourly determination of urine output. All animals were given heparin to maintain an activated clotting time of greater than twice control.

The deflated PABC device was positioned in the pulmonary artery as described below. Baseline hemodynamic parameters including heart rate, arterial pressure, central venous pressure, right ventricular pressure, pulmonary artery pressures, pulmonary capillary wedge pressure, cardiac output, positive RV dP/dt, and negative RV dP/dt were recorded. Under baseline conditions, arterial blood gases were measured and blood samples were analyzed for determination of creatine kinase level. A serum sample was also obtained for liver function tests and measurement of electrolytes, blood urea nitrogen, and creatinine levels. Anesthesia was continued for 12 hours, during which time hourly determinations of hemodynamic parameters were made. Arterial blood gases were monitored hourly and appropriate changes in ventilator rate were made. Serum samples for liver function tests and measurement of cardiac enzymes, electrolytes, blood urea nitrogen, and creatinine were obtained at 6 and 12 hours. After 12 hours of continuous monitoring, control animals were sacrificed using an overdose of pentobarbital and potassium chloride as per the Yale Animal Care and Use Committee protocols. The heart and lungs were excised as a block for pathologic examination. Both kidneys and the liver were also removed for pathologic examination. All organs were fixed in a 10% solution of formaldehyde.

The second group of 6 animals underwent 12 hours of PABC. Full hemodynamic monitoring was instituted as in control animals. The left femoral vein was exposed proximally and distally for subsequent introduction of the PABC device. Under fluoroscopic guidance the pulmonary artery was cannulated from the left femoral vein using a second, standard pulmonary artery catheter with a 1-mL balloon. Once in place, a wire was inserted through the central lumen of this pulmonary artery catheter. The catheter was withdrawn, leaving the wire in place. Subsequently, the PABC device was inserted over the wire under fluoroscopic guidance. Radiopaque markers at the tip of the PABC device permitted visualization within the pulmonary artery. The proximal third of the device was positioned in the main pulmonary artery and the distal two thirds in either the right or left pulmonary artery (Fig 1). An injection of Renograffin-76 (diatrizoate meglumine and diatrizoate sodium injection; Squibb Diagnostics, New Brunswick, NJ) was then administered through the central lumen of the PABC device; visualiza-

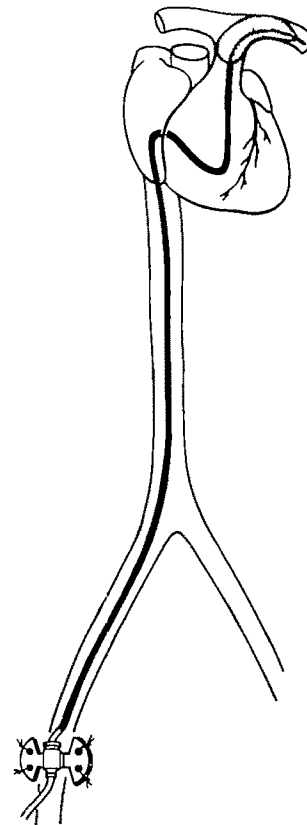


Fig 1. Position of pulmonary artery balloon counterpulsation device during counterpulsation. Proximal third of balloon is located in main pulmonary artery. Distal two thirds of balloon are located in left or right pulmonary artery.

tion of a branch of the right or left pulmonary artery confirmed appropriate device position.

At right anterolateral thoracotomy, the device was inflated gently and position was confirmed by palpation. A right ventricular catheter for measurement of right ventricular pressure, positive RV dP/dt, and negative RV dP/dt was placed through the right ventricular free wall, and the anterolateral thoracotomy was closed. A suprapubic cystostomy was placed.

Baseline parameters were measured as in the control group of animals. Pulmonary artery balloon counterpulsation was then initiated using a Datascope System 83 drive (Datascope, Inc). An arterial pressure wave form recorded from the distal port of the PABC device was used to time counterpulsation. Balloon inflation began just after pulmonary valve closure as indicated by the dicrotic notch in the pulmonary artery trace, and deflation began just before the following systolic contraction of the heart. Counterpulsation continued for 12 hours. Hemodynamic and serum studies were then obtained as in the control group. At the conclusion of 12 hours of counterpulsation, animals were sacrificed as described above. Heart and lungs were excised as a block for pathologic examination, as were both kidneys and the liver. All organs were fixed in 10% formalin for pathologic examination. At the conclusion of each experiment, the PABC device was withdrawn and examined for clot or damage.

Table 1. Hemodynamic Parameters in Control Animals ($n = 6$) and Experimental Animals ($n = 6$) at 12 Hours

Index	Control (PABC device inserted but not activated) ^a	Experimental (PABC device inserted and activated) ^a	p Value ^b	95% Confidence Limits
Heart rate (beats/min)	142 $\pm$ 8.0	149 $\pm$ 5.0	0.48	-28.9, 14.5
Central venous pressure (mm Hg)	4.0 $\pm$ 2.0	5.5 $\pm$ 1.2	0.65	-6.1, 4.1
Right ventricular end-diastolic pressure (mm Hg)	5.5 $\pm$ 1.7	5.2 $\pm$ 1.3	0.36	-2.7, 6.7
+dP/dt (mm Hg/s)	1,733 $\pm$ 393	1,417 $\pm$ 353	0.60	-1,050, 1,683
-dP/dt (mm Hg/s)	1,433 $\pm$ 384	1,267 $\pm$ 349	0.77	-1,513, 1,180
Cardiac index (L/min $\cdot$ m ²)	4.95 $\pm$ 0.84	4.52 $\pm$ 0.60	0.69	-1.6, 3.1
Pulmonary vascular resistance (Wood units)	3.05 $\pm$ 0.70	2.72 $\pm$ 0.44	0.70	-1.5, 2.2

^a Mean $\pm$ standard error. ^b Two-sample t test.

dP/dt = first time derivative of right ventricular pressure; PABC = pulmonary artery balloon counterpulsation.

All results were indexed using basal surface area as calculated using the equation [7]: canine basal surface area = $0.112 \times 2/3$ body weight in kilograms.

All animals received humane care in compliance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research and the "Guide for the Care and Use of Laboratory Animals" prepared by the National Academy of Sciences and published by the National Institutes of Health (NIH publication No. 85-23, revised 1985). The Yale University Animal Care and Use Committee also approved and regulated the use of all animals.

All data are presented as mean $\pm$ standard error. The two-sample t test and the paired t test were used to test differences between the groups. A p value of less than 0.01 was considered significant.

Results

All 12 animals completed the protocol without operative death. Data from the 6 control animals were pooled for analysis, as were data from the 6 experimental animals.

Hemodynamic Effects

A comparison of the hemodynamic parameters in the control group after 12 hours with parameters in the experimental group after 12 hours of PABC is presented in Table 1. No difference in heart rate, central venous pressure, right ventricular end-diastolic pressure, positive and negative RV dP/dt, cardiac index, or pulmonary vascular resistance was detected ($p > 0.01$). A second comparison of hemodynamics within the experimental group of animals just after PABC initiation (0 hours) and after 12 hours of PABC revealed no statistically significant differences in any of these hemodynamic parameters at the p less than 0.01 level (Table 2). A third comparison of baseline and 12-hour hemodynamic parameter differences in control and experimental groups using a two-sample t test revealed both groups to be comparable at baseline conditions (Table 3), indicating that the lack of significant changes in hemodynamic parameters at 12 hours was not due to differences between the two groups of animals under baseline conditions.

There was, however, a marked increase in both dia-

Table 2. Hemodynamics in Experimental Animals After Initiation of PABC (0 Hours) and After 12 Hours of PABC ($n = 6$)

Index	0 Hours ^a	12 Hours ^a	p Value ^b	95% Confidence Limits
Heart rate (beats/min)	126 $\pm$ 7.0	149 $\pm$ 5.0	0.07	-49.0, 3.0
Central venous pressure (mm Hg)	5.7 $\pm$ 1.1	5.0 $\pm$ 1.2	0.36	-1.0, 2.4
Right ventricular end-diastolic pressure (mm Hg)	4.2 $\pm$ 0.6	3.5 $\pm$ 1.3	0.53	-1.9, 3.2
+dP/dt (mm Hg/s)	1,317 $\pm$ 158	1,417 $\pm$ 353	0.75	-860, 660
-dP/dt (mm Hg/s)	1,083 $\pm$ 156	1,267 $\pm$ 349	0.67	-1,219, 852
Cardiac index (L/min $\cdot$ m ²)	4.38 $\pm$ 0.64	4.52 $\pm$ 0.61	0.87	-2.2, 1.9
Pulmonary vascular resistance (Wood units)	1.64 $\pm$ 0.22	2.72 $\pm$ 0.44	0.11	-2.5, 0.3

^a Mean $\pm$ standard error. ^b Paired t test.^d dP/dt = first time derivative of right ventricular pressure; PABC = pulmonary artery balloon counterpulsation.

Table 3. Baseline and 12-Hour Hemodynamic Parameter Differences in Control and Experimental Animals

Index	Difference Between Baseline and 12- Hour Values in Control Animals ^a	Difference Between Baseline and 12- Hour Values in Experimental Animals ^a	p Value ^b
Heart rate (beats/min)	-11.6 ± 9.2	-23.0 ± 10.1	0.43
Central venous pressure (mm Hg)	-1.3 ± 0.3	0.7 ± 0.7	0.09
Right ventricular end-diastolic pressure (mm Hg)	-4.0 ± 1.1	2.7 ± 1.0	0.10
+dP/dt (mm Hg/s)	-566.7 ± 240.4	-100.0 ± 295.5	0.34
-dP/dt (mm Hg/s)	-566.7 ± 133.3	183.3 ± 402.8	0.54
Cardiac index (L/min · m ²)	0.18 ± 1.01	-0.14 ± 0.79	0.60
Pulmonary vascular resistance (Wood units)	0.95 ± 0.66	-1.08 ± 0.55	0.89

^a Mean ± standard error. ^b Two-sample *t* test.

dP/dt = first time derivative of right ventricular pressure.

stolic augmentation and systolic unloading within the experimental group after 12 hours of PABC as compared with shortly after PABC initiation (0 hours). The amount of diastolic augmentation increased from 0.5 ± 0.5 mm Hg just after PABC initiation to 5.0 ± 1.1 mm Hg after 12 hours ($p < 0.01$). The amount of systolic unloading also increased from 1.5 ± 1.0 mm Hg at PABC initiation to 9.5 ± 1.6 mm Hg after 12 hours of counterpulsation ($p < 0.01$). A typical tracing after 12 hours in the experimental group is shown in Figure 2. It should be noted that pulmonary vascular resistance did not change significantly over the same period.

Arterial Blood Gas Analysis

No detrimental effects on pulmonary function as determined by arterial blood gas analysis were noted. The pH in the control group (7.39 ± 0.02) was not significantly different than that in the experimental group (7.32 ± 0.02) after 12 hours ($p > 0.01$). Nor were carbon dioxide tension or oxygen tension different ($p > 0.01$) in the control group as compared with the experimental group of animals after 12 hours (29 ± 2.8 versus 31 ± 2.6 mm Hg and 327 ± 39 mm Hg versus 415 ± 39 mm Hg, respectively). Within the experimental group there were no significant differences ($p > 0.01$) noted between the pH, carbon dioxide tension, or oxygen tension at 0 or 12 hours (Table 4). (Although changes in ventilation were made as the exper-

iment progressed, no animal required a ventilatory rate greater than 10 breaths per minute; oxygenation was always with an inspired oxygen fraction of 0.40.)

Serum Analysis for Creatine Kinase, Renal Function, and Liver Function

Creatine kinase levels and liver function test results (including levels of alkaline phosphatase, serum glutamic-oxaloacetic transaminase, total bilirubin, and indirect bilirubin) were obtained at 6 and 12 hours in 3 control animals and 5 experimental animals (Veterinary Labs of America, Lindenhurst, NY). None showed an increase in the MB fraction of creatine kinase. Blood urea nitrogen and creatinine levels were normal in all animals. Alkaline phosphatase and serum glutamic-oxaloacetic transaminase levels were frequently elevated in both control and experimental animals. Total bilirubin and indirect bilirubin levels were normal in all animals.

Pathology

At the conclusion of each experiment the liver, both kidneys, and the heart-lung block were excised for pathologic examination. Gross examination revealed no obvious pathologic structural abnormalities of any organ. Sectioning of the heart-lung blocks revealed all except one to be without abnormalities attributable to the PABC device. One animal, in which the balloon leaked on

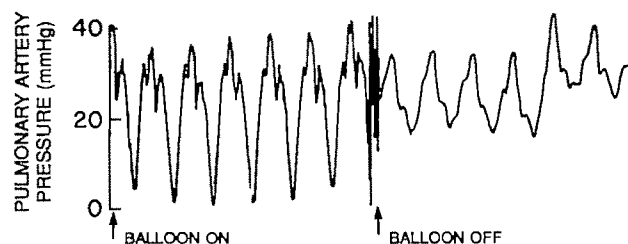
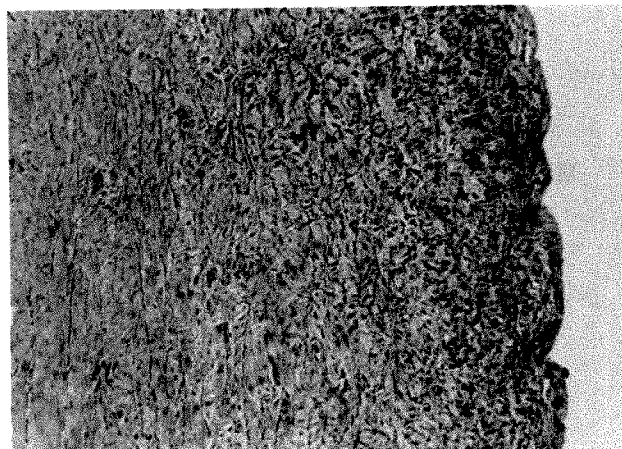


Fig 2. Typical pulmonary artery pressure trace after 12 hours. Trace was recorded from pulmonary artery catheter in pulmonary artery without pulmonary artery balloon counterpulsation device.

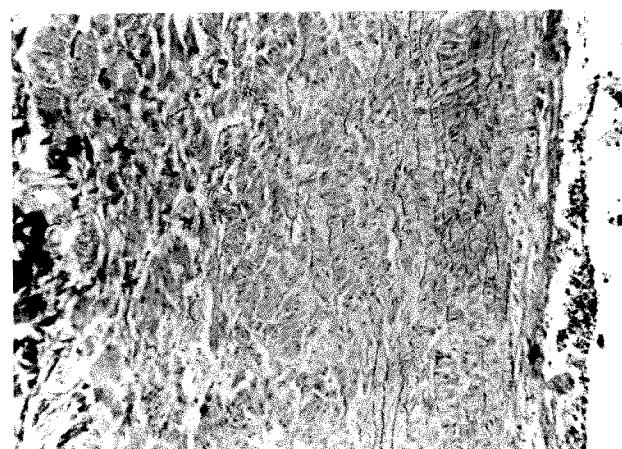
Table 4. Arterial Blood Analysis in Experimental Animals After Initiation of PABC (0 Hours) and After 12 Hours of PABC

Index	0 Hours	12 Hours	p Value ^a
pH	7.33 ± 0.02	7.32 ± 0.02	NS
pCO ₂ (mm Hg)	30 ± 2.8	31 ± 2.8	NS
pO ₂ (mm Hg)	351 ± 50	415 ± 39	NS

^a Paired *t* test.NS = not significant; PABC = pulmonary artery balloon counterpulsation; pCO₂ = carbon dioxide tension; pO₂ = oxygen tension.



A



B

Fig 3. Pathologic specimens from both control and experimental animals. (A) Pulmonary artery from a control animal. There is no evidence of thrombus or endothelial damage. The media is normal. (Hematoxylin and eosin, $\times 100$ before 47% reduction.) (B) Pulmonary artery in region of contact with balloon from an experimental animal. Red blood cells within a fine fibrin mesh are adherent to the endothelial surface at right of photomicrograph. The media of the vessel is undamaged. (Hematoxylin and eosin, $\times 100$ before 48% reduction.)

manipulation of the pulmonary artery just after the experiment's conclusion (to obtain specimens for pathologic analysis), had gross hemorrhage of the right main pulmonary artery adventitia.

Microscopic examination of the pulmonary arteries was unremarkable in all cases except for the 1 animal in which the balloon ruptured after the experiment's conclusion. Minimal aggregation and adherence of various blood cells to pulmonary artery endothelium occurred. None of the microscopic findings were clinically significant. Evidence of endothelial damage or erosion was absent microscopically. A typical microscopic section from a control animal is compared with that of an experimental animal in Figure 3. Thrombosis within the pulmonary vasculature surrounded by an old bronchopneumonia was found in 1 animal but was not related to the PABC device. No other pulmonary thrombi were found.

Pulmonary artery balloon counterpulsation devices removed at the conclusion of each experiment were carefully examined for any evidence of clot or thrombus formation, and no such evidence was found.

Comment

Pulmonary artery balloon counterpulsation has been effective in several experimental models [4]. As early as 1970, Kralios and associates [5] demonstrated the efficacy of PABC in sheep using a 25-mL balloon. In a model of right ventricular failure caused by corn starch embolization, cardiac output increased and pulmonary vascular resistance decreased with PABC. This report was followed by one from Spotnitz and associates [6] using a piston pump for counterpulsation of the pulmonary artery in dogs. Their short-term experiment (10 minutes) showed that synchronized counterpulsation significantly reduced peak right ventricular systolic pressure in normal dogs and in dogs with pulmonary hypertension produced by pulmonary artery constriction. Miller and associates [1] reported the first clinical use of a system for PABC in 1980. They employed a synthetic vascular graft sutured to the main pulmonary artery in an end-to-side fashion as a reservoir for a 35-mL balloon. This method of PABC was used in tandem with an intraaortic balloon to ameliorate severe biventricular failure after coronary artery bypass grafting. Significant hemodynamic improvement occurred, although the patient eventually died. Using a similar system, Flege and colleagues [2] reported the first successful use of PABC for severe right ventricular failure after mitral valve replacement. The technique was unwieldy, however, and has not been widely accepted or used.

Several other authors have shown PABC to be effective in short-term models. Pulmonary artery balloon counterpulsation is effective in increasing right ventricular output in swine with right ventricular failure induced by propranolol while the left heart is supported on left heart bypass [8]. Cardiac output increased from 0.4 to 0.7 L/min in this model. Another model in swine showed the efficacy of 40 minutes of PABC in right ventricular failure produced by right ventriculotomy; right ventricular end-diastolic pressure decreased 50% and cardiac output increased by 44% [9]. A longer term experiment performed by Jett and associates [10, 11] in lambs revealed increased cardiac output, decreased right ventricular peak systolic pressure, and decreased right ventricular end-diastolic pressure with counterpulsation.

With such experimental and clinical evidence for the effectiveness of PABC, a question of primary importance is whether the technique can be adapted for easy and safe clinical use. Our objective in developing and testing the 8-mL PABC device was to demonstrate its ease of use, safety, and hemodynamic efficacy.

Unlike previous devices used for PABC, this one, with its smaller catheter caliber (similar to the widely used intraaortic balloon), was easily inserted through the femoral vein into the pulmonary artery in all animals. The technique is similar to insertion of a pulmonary artery

catheter, although device rigidity makes placement under fluoroscopic guidance mandatory. Device position was easily confirmed with injection of radiopaque material through the central port of the catheter. Once in place, the balloon did not migrate proximally or distally in any of our experiments. Ventricular ectopy was not significant, although occasional premature ventricular contractions were noted.

Diastolic augmentation and systolic unloading were minimal just after initiation of counterpulsation. This is not unexpected; intraaortic balloon counterpulsation also produces minimal effects in normal animals, and similar findings have been reported in pulmonary artery counterpulsation [6]. Nevertheless, diastolic augmentation and systolic unloading increased over time and were statistically significant at 12 hours. Previous animal studies have not addressed this phenomenon, as most were of much shorter duration. Obviously, future studies must address the question of whether PABC can ameliorate or reverse experimentally induced right ventricular failure.

We selected a balloon size of 8 mL for our 25- to 35-kg animals. Although others have used balloons as large as 25 mL in pigs [12], our preliminary investigations using balloons of larger size frequently resulted in right ventricular outflow tract obstruction with subsequent right ventricular dilation and failure, particularly if any mistiming of balloon inflation and deflation occurred. The relatively small balloon may be one reason we detected little hemodynamic improvement initially. However, our smaller balloon size minimized the problem of improper timing of inflation or deflation (no episode of right ventricular dilation occurred) and still provided dramatic hemodynamic effects after 12 hours. Placement of the device close to the pulmonary valve is important. In contrast to intraaortic balloon counterpulsation, the pulmonary artery balloon can be placed very close to the ventricular outflow tract, thereby magnifying the effect of a relatively small balloon [13].

Previous reports have suggested that pulmonary vascular thrombosis may be produced by counterpulsation [14]. As prophylaxis against thrombosis, activated clotting time was kept at least twice control values in our series, and pathologic studies revealed no evidence of thrombosis. Balloon position was confirmed with fluoroscopy after placement and was probably important in avoiding pulmonary valve or artery damage. After 12 hours of counterpulsation, no pulmonary valve or pulmonary artery intimal damage occurred in any animal. Although a longer period of 24 to 72 hours of observation would be desirable, considerations concerning the humane care of animals make this impossible at our institution.

Analysis of creatine kinase levels revealed no elevation at 6 or 12 hours in any animal. Arterial blood gas samples revealed no deterioration in oxygenation or ventilation with counterpulsation of 12 hours duration. Thus, no biochemical evidence of cardiopulmonary damage was found after 12 hours of counterpulsation.

In summary, PABC is a promising technique for the treatment of right ventricular failure through afterload reduction. It is possible to achieve diastolic augmentation and systolic unloading after placement of an appropriately sized device through the femoral vein. Counterpulsation is free of detrimental effects on cardiac function after 12 hours. Further studies on a long-term model of right ventricular failure are warranted before widespread clinical use.

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Age and Protection of the Ischemic Myocardium: Is Alkaline Cardioplegia Appropriate?

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Hypothermic alkaline pharmacologic cardioplegia used in pediatric cardiac surgery may be less than satisfactory despite its benefits in adults. We determined whether the pH (7.8) of standard St. Thomas' II cardioplegic solution contributes to inadequate protection of the ischemic immature heart and whether the effect is age-related. Modified hypothermic St. Thomas' II solution (pH range, 4.8 to 8.8) was compared with hypothermic bicarbonate buffer alone (pH 7.25) in protecting the ischemic immature (7 to 10 days old) and mature (12 months old) rabbit heart. Isolated hearts ($n = 6$ per group) were perfused with bicarbonate buffer, and aortic flow was measured before hypothermic (14°C) ischemia (immature hearts: 4 hours; mature hearts: 3 hours). Hearts were reperfused, and enzyme leakage and recovery of function were measured. In the immature heart, a bell-shaped dose-response profile was observed for pH and

recovery of aortic flow but not for postischemic creatine kinase leakage. Optimal recovery of aortic flow ($98\% \pm 3\%$) occurred at pH 6.8, which was greater than protection with hypothermia alone ($82\% \pm 4\%$; $p < 0.05$) and standard St. Thomas' II solution ($72\% \pm 2\%$; $p < 0.05$). In the mature heart, a bell-shaped dose-response curve existed for recovery of aortic flow and a U-shaped curve existed for creatine kinase leakage. Again, optimal recovery of aortic flow ($84\% \pm 5\%$), which was superior to that with standard St. Thomas' II solution ($60\% \pm 8\%$; $p < 0.05$), and minimal enzyme leakage also occurred at pH 6.8, as did the least enzyme leakage ($p < 0.05$). The pH of standard St. Thomas' II solution is suboptimal to protect the ischemic immature and mature myocardium, and protection is improved by mild acidification.

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Clinical application of hypothermic pharmacologic cardioplegia in pediatric cardiac surgery has been reported to be less than satisfactory [1] despite its well-known benefits in adults [2]. We [3] have shown that protection of the ischemic immature rabbit heart with hypothermic Krebs bicarbonate buffer alone is better than with hypothermic St. Thomas' II cardioplegic solution. This effect is age [3] and species [4] dependent, but it is independent of the oxygen content in the preischemic perfusate [5]. Our experimental finding is of concern, as St. Thomas' II cardioplegic solution is currently in use during pediatric cardiac operations.

We have hypothesized that the existing concentration of one or more of the components of St. Thomas' II solution is less than optimal or even detrimental to the protection of the ischemic immature heart during hypothermic ischemia. The existing calcium concentration of St. Thomas' II solution is one component responsible for inadequate protection of the ischemic immature rabbit heart [6]. However, the greatest difference in the concentration of an individual component between hypothermic Krebs buffer and St. Thomas' II solution is that of pH. The pH of Krebs buffer as determined at 14°C is 7.25, and the

pH of St. Thomas' II solution, 7.8. This value for St. Thomas' II solution was based on theoretical considerations relating to the anticipated development of acidosis during ischemia in the mature heart [7] as well as the alkaline shift of the pK of water with hypothermia [8, 9]. The suggestion that an alkaline pH is best when formulating cardioplegic solutions has been widely adopted by clinicians and investigators. However, we are aware of no studies that confirm whether myocardial protection of either immature or mature myocardium with St. Thomas' II solution is optimal at this alkaline pH, or determine the interaction of pH with the calcium component of this cardioplegic solution.

The objectives of this study therefore were (1) to determine whether the pH of St. Thomas' II solution contributes to inadequate protection of the ischemic immature heart, (2) to determine whether this effect is age-related, (3) to assess the impact of modifying pH on the calcium activity of the cardioplegic solution, and (4) to determine the effect of temperature on the measurement of pH of the coronary perfusates.

Material and Methods

Experimental Animals

Immature New Zealand white rabbits ($n = 69$) aged 7 to 10 days were obtained from a *Pasteurella*-free breeding colony within the Medical College of Wisconsin. Between 6 and 10 kits (young rabbits) were produced per litter. To avoid dehydration, we allowed mature animals free ac-

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Table 1. Baseline Measurements^{a,b}

Variable	Immature Heart	Mature Heart
Body weight (kg)	0.11 ± 0.01	4.31 ± 1.37
Heart wet weight (g)	0.7 ± 0.2	15.6 ± 3.2
Mean aortic pressure (mm Hg)	42 ± 9	88 ± 7
Heart rate (beats/min)	291 ± 11	188 ± 7
Aortic flow (mL/min)	30 ± 6	118 ± 11
Coronary flow (mL/min)	8 ± 2	46 ± 9

^a Data are shown as the mean ± the standard deviation pooled from all animals used in the study. ^b There were no significant differences in preischemic control values between experimental groups. With the exception of body weight and mean aortic pressure, all data were derived from isolated hearts.

cess to water and kept immature animals with their mothers until just before the induction of anesthesia. Mature New Zealand white rabbits ($n = 72$) aged 12 months were obtained from a commercial breeder. Data on body weight and heart weight for the two age groups are shown in Table 1. Animals used in this study received humane care in compliance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research and the "Guide for the Care and Use of Laboratory Animals" prepared by the National Academy of Sciences and published by the National Institutes of Health (NIH publication No. 85-23, revised 1985).

Heparin sodium (150 IU/kg) was administered intraperitoneally before the administration of anesthetics. Anesthesia was induced and maintained with halothane (4.0% and 1.5%, respectively). The chest was opened, and the pericardium was removed. The aorta and inferior vena cava were isolated, and the heart was rapidly excised and placed in ice-cold Krebs-Henseleit bicarbonate buffer. The time from the opening of the chest to the excision of the heart was less than 1 minute.

Perfusion System

The standard isolated working heart preparation (Biomedix, Elm Grove, WI), described initially by Neely and colleagues [10], was modified to provide a physiological work load and temperature suitable for immature and mature rabbits. The preparation has been described in detail previously [3, 4]. Essentially, it is a left heart preparation in which oxygenated Krebs-Henseleit bicarbonate buffer [11] supplemented with glucose enters the cannulated left atrium at a pressure of 6 mm Hg for immature hearts and 9 mm Hg for mature hearts. The perfusate then passes to the left ventricle, from which it is spontaneously ejected through the cannulated aorta against a compliant hydrostatic head of mean pressure of 42 mm Hg for immature hearts and 88 mm Hg for mature hearts. These pressures are physiologic for immature and mature rabbit hearts [3].

Hearts in each test group in which the control hemodynamic performance deviated by one standard deviation or more from the mean values shown in Table 1 were

excluded from the study. This exclusion criterion resulted in rejection of 9 of 69 immature hearts and 12 of 72 mature hearts. Additional hearts were perfused until 6 were available for analysis of function. The hearts and perfusates were kept in temperature-controlled chambers to maintain myocardial temperature at the desired level. During all periods of ischemia, the heart was immersed in ungasped physiological saline solution.

Perfusion Media

The standard perfusion medium used was Krebs-Henseleit bicarbonate buffer [11] (pH 7.41 at 39°C and 7.25 at 14°C when saturated with 95% oxygen and 5% carbon dioxide [12]) in which the calcium content was reduced to 1.8 mmol/L. To this was added glucose (11.1 mmol/L). The cardioplegic solution used was St. Thomas' II solution [13]. Compositions of the individual perfusates are shown in Table 2. Glucose was excluded from all perfusates during hypothermic Langendorff perfusion of the coronary network immediately before and throughout ischemia. The pH of St. Thomas' II solution (normally 7.8) was modified from 4.80 to 8.80 by manual titration using hydrochloric acid/sodium hydroxide. During the preparation of all calcium-containing solutions, precautions were taken to prevent the precipitation of calcium [14] by gassing the solutions with 5% carbon dioxide. Oxygen content of the perfusates was measured using a Lex-O₂-Con fuel cell analyzer (Lexington Instruments, Waltham, MA) calibrated against room air at room temperature. All measurements of pH were made using a Data Tech 14 pH meter (Data Tech Systems Ltd, Victoria, BC, Canada) calibrated with known pH standards at the temperature of the coronary perfusate. The total calcium content of the coronary perfusate was measured using an IL-357 atomic absorption spectrophotometer (Instrumentation Labora-

Table 2. Composition of Coronary Perfusates

Constituent	Krebs-Henseleit Bicarbonate Buffer (mmol/L)	St. Thomas' Hospital Cardioplegic Solution II (mmol/L)
NaCl	118.5	110.0
NaHCO ₃	25.0	10.0
KCl	4.8	16.0
KH ₂ PO ₄	1.2	...
MgSO ₄ · 7 H ₂ O	1.2	...
MgCl ₂ · 6 H ₂ O	...	16.0
CaCl ₂ · 2 H ₂ O	1.8	1.2
pH ^{a,b}	7.41 ± 0.01	7.80 ± 0.01
Po ₂ (mm Hg) ^c	592 ± 16	180 ± 11
O ₂ content (mL/dL) ^{b,d}	2.30 ± 0.1	0.92 ± 0.1

^a The pH of Krebs-Henseleit bicarbonate buffer was 7.41 at 39°C and 7.25 at 14°C when gassed with 5% CO₂. The pH of the unmodified cardioplegic solution was titrated to 7.80 at 14°C using HCl/NaOH. ^b Data on pH and oxygen content represent the mean ± the standard deviation of eight observations. ^c The Po₂ of the coronary perfusates at 14°C was determined at 38°C. ^d The oxygen content of the coronary perfusates at 14°C was determined at room temperature.

Po₂ = oxygen tension.

tories, Inc, Lexington, MA). Before use, all perfusion fluids were filtered through cellulose acetate membranes with a pore size of 5.0 μ m.

Perfusion Sequence

pH AND PROTECTION OF THE IMMATURE HEART. The following experiments were performed in a random manner in ten groups of 6 immature hearts each to test the null hypothesis that protection of the ischemic immature rabbit heart is unaffected by the pH of the coronary perfusate. Immediately after aortic cannulation, the hearts were perfused in the Langendorff [15] mode for a 15-minute stabilization period during which the left atrium was cannulated. The hearts were then converted to the working [10] mode for 35 minutes. During this period, control values for aortic and coronary flow rates, heart rate, and electrical activity were recorded under steady-state conditions. This was followed by a single 3-minute period of hypothermic (14°C) coronary perfusion in the Langendorff mode with either Krebs-Henseleit bicarbonate buffer (pH 7.25) or the modified cardioplegic solution (pH varied from 4.8 to 8.8). The 3-minute period of preischemic coronary perfusion was carried out with perfusion pressure fixed at 60% of the mean aortic pressure for the immature rabbit heart. This reduced pressure was selected to minimize the development of iatrogenic myocardial edema while maintaining adequate volume of perfusion and cooling of the heart.

Hearts were then subjected to global hypothermic (14°C) ischemia for 4 hours. This is the target temperature commonly achieved and maintained clinically during cardioplegic arrest of the immature heart [1]. After the ischemic period, hearts were reperfused for 15 minutes in the Langendorff mode with the entire coronary effluent collected for the determination of creatine kinase activity. Hearts were then converted to the working mode for 35 minutes, during which time the various indices of function were measured under steady-state conditions and expressed as a percentage of the preischemic control values. Each heart thus served as its own control.

pH AND PROTECTION OF THE MATURE HEART. The following experiments were performed in random order in ten groups of 6 mature hearts each to test the null hypothesis that protection of the ischemic mature rabbit heart is unaffected by the pH of the coronary perfusate. The protocol used for this experiment was the same as that described for the immature hearts except that the mature hearts were subjected to 3 hours of ischemia.

(1) MEASUREMENT OF INDICES OF FUNCTION. Aortic flow was defined as the ability of the heart to eject perfusate against the hydrostatic head, with flow rate measured using an in-line analog flowmeter (Biomedix). Coronary flow rate was defined by timed collections of the effluent from the right heart into a graduated cylinder. Electrical activity and heart rate were evaluated from electrocardiographic recordings obtained from leads attached to the aortic and atrial cannulas.

(2) CREATINE KINASE DETERMINATION. The entire coronary effluent during the Langendorff reperfusion period was collected in a graduated cylinder surrounded by ice. Bovine serum albumin was added to the cylinder to achieve a final concentration of 5% (wt/vol) to stabilize the enzyme. After its volume was recorded and the contents of the flask were mixed, an aliquot of the coronary effluent was taken for the determination of total creatine kinase (ATP: creatine *N*-phosphotransferase) [16] activity.

pH AND CALCIUM ACTIVITY OF THE CARDIOPLEGIC SOLUTION. The impact of pH on the calcium activity of the cardioplegic solution at 14°C was measured using a calcium ion-selective electrode mounted inside a beaker containing 1,000 mL of the cardioplegic solution. The solution was maintained at 14°C and continuously stirred. The calcium ion concentration of the cardioplegic solution containing 1.2 millimoles of total calcium per liter was measured under steady-state conditions in eight separate experiments during a gradual change in solution pH from 4.8 to 9.3 over 60 minutes.

Calcium activity at 14°C was determined using a fresh calcium ion-selective electrode (model 93-20; Orion Research Inc, Cambridge, MA) and a liquid-junction reference electrode (Orion model 90-01). Electrode calibration was carried out using calcium standards of identical ionic strength with those of the cardioplegic solution. This allowed the calcium ion concentration to be reported as free calcium ion activity. The change in electrical potential in these solutions developed between the calcium ion and reference electrode were measured using a digital voltmeter. Steady-state changes in potential were obtained within 1 minute. Interference by pH with the measurement of calcium ion activity was determined by changing the pH of the calcium calibration solutions. In six experiments, the mean shift in the calibration curve for 1.0 millimoles of calcium per liter per unit rise in pH was not significant ($p > 0.1$). The total (elemental) calcium content of the cardioplegic solution was determined using an IL-357 atomic absorption spectrophotometer (Instrumentation Laboratories).

IMPACT OF TEMPERATURE ON MEASUREMENT OF pH OF THE CORONARY PERFUSATE. The effect of temperature on the measurement of the pH of both St. Thomas' II solution and Krebs-Henseleit bicarbonate buffer was determined over the range 10° to 40°C. For each temperature studied, the pH electrode was recalibrated against known standards at each temperature. Steady-state levels in pH were obtained within 1 minute of achieving the desired temperature.

Expression of Results

Aortic flow rate was expressed as a percentage of its preischemic control value. Creatine kinase leakage, corrected for the volume of coronary effluent collected during the Langendorff reperfusion period, was expressed as international units released per 15 minutes per gram of dry weight. Calcium ion concentration was expressed as free calcium ion activity in millimoles per liter. Total calcium content was expressed in millimoles per liter.

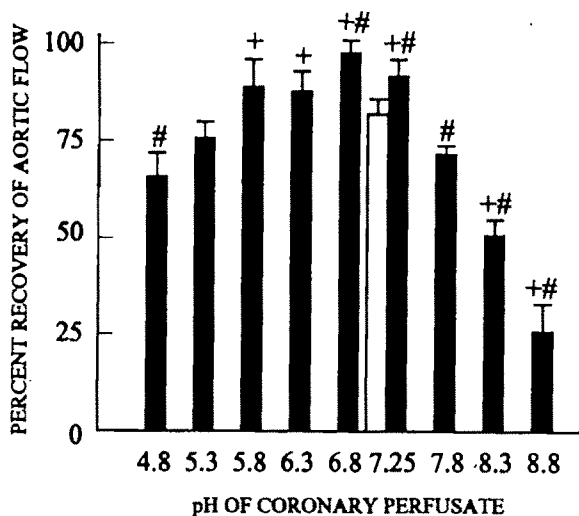


Fig 1. pH and cardioplegic protection in the immature heart: relationship between postischemic recovery of aortic flow and pH of pre-ischemic perfusate. Closed histograms represent data from hearts protected by hypothermia plus cardioplegia. The open histogram represents data from hearts protected by hypothermia alone. Data shown represent the mean $\pm$ the standard deviation from 6 hearts per group. (+ = $p < 0.05$, hypothermia plus cardioplegia: pH 7.8 versus modified pH; # = $p < 0.05$, hypothermia alone versus hypothermia plus cardioplegia.)

Six hearts were used for each condition studied, and the results were expressed as the mean $\pm$ the standard deviation of the mean. Statistical analysis was performed using the Kruskal-Wallis nonparametric analysis of variance by ranks as a first step, and where this proved significant, the Mann-Whitney test was used as a second step to identify which groups were significantly different [17]. Significance was accepted at the level of p less than 0.05.

Results

Baseline Measurements

Baseline data for the two age groups are shown in Table 1. The hemodynamic stability of the model was assessed by perfusing hearts in the working mode for 160 minutes with nonrecirculating perfusate. No significant changes in heart rate or aortic flow occurred until after 90 minutes of perfusion in immature hearts and 110 minutes in mature hearts. In the studies described that test our hypotheses, the hearts were perfused in the working mode for a maximum of 70 minutes, well within the stability limits of the preparation.

pH and Protection of Immature Heart

FUNCTIONAL RECOVERY. Figure 1 illustrates several findings with respect to the pH of the coronary perfusate and recovery of aortic flow in immature hearts subjected to hypothermic ischemia. First, recovery of aortic flow in immature hearts protected by hypothermia alone ($82\% \pm 4\%$) was better than with the standard (pH 7.8) St. Thomas' II solution ($72\% \pm 2\%$) ($p < 0.05$). Second, a

bell-shaped dose-response profile for pH and functional recovery was observed. As the pH of St. Thomas' II solution progressively decreased from its normal value of 7.8, the percent recovery of aortic flow increased. Optimal recovery of aortic flow with the modified cardioplegic solution occurred at a pH of 6.8. Recovery of aortic flow in this group was $98\% \pm 3\%$. This was significantly greater than with protection provided by either hypothermia alone ($82\% \pm 4\%$) or standard St. Thomas' II solution ($72\% \pm 2\%$) (both, $p < 0.05$). When the pH of the cardioplegic solution was increased from its normal value of 7.8, there was a progressive decline in recovery of aortic flow to $26\% \pm 7\%$ at pH 8.8. The electrical systems of immature hearts tolerated ischemia well regardless of the broad range of pH studied. All hearts returned spontaneously to normal sinus rhythm within 30 seconds after reperfusion. There were no significant changes in heart rate on reperfusion for any of the hydrogen ion concentrations investigated.

POSTISCHEMIC ENZYME LEAKAGE. Figure 2 shows that for immature hearts protected with hypothermia alone (pH 7.25), creatine kinase leakage during the 15-minute Langendorff reperfusion period was 59 ± 19 IU/g dry weight. When hearts were protected by hypothermia plus unmodified St. Thomas' II solution (pH 7.8), creatine kinase leakage was 70 ± 9 IU/g dry weight ($p =$ not significant). In hearts where the pH of the cardioplegic solution was modified over the range 4.8 to 8.8, there were no differences in postischemic creatine kinase leakage compared with that in hearts protected by hypothermia alone and hypothermia plus the unmodified cardioplegic solution.

pH and Protection of the Mature Heart

FUNCTIONAL RECOVERY. Figure 3 shows the relationship between the pH of the coronary perfusate and recovery of

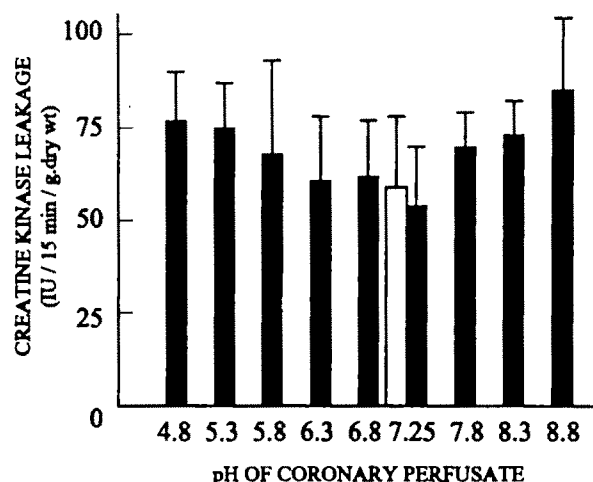


Fig 2. pH and cardioplegic protection in the immature heart: relationship between postischemic creatine kinase leakage and pH of the pre-ischemic perfusate. Closed histograms represent data from hearts protected by hypothermia plus cardioplegia. The open histogram represents data from hearts protected by hypothermia alone. Data shown represent the mean $\pm$ the standard deviation from 6 hearts per group.

aortic flow in mature hearts. No hearts protected with hypothermia alone were able to generate aortic flow or even sufficient ventricular pressure to maintain the hydrostatic column of perfusate. Protection of mature hearts with the standard St. Thomas' II solution resulted in $60\% \pm 8\%$ recovery of aortic flow. The bell-shaped dose-response profile for pH and recovery of aortic flow observed for mature hearts was similar to that observed for immature hearts. As the pH of the cardioplegic solution was reduced from its standard value of 7.8, recovery of aortic flow progressively increased. Optimal recovery of aortic flow with the modified cardioplegic solution occurred at a pH of 6.8. Recovery of aortic flow at this slightly acidic pH was $84\% \pm 5\%$; this was greater ($p < 0.05$) than in hearts protected by the standard cardioplegic solution ($60\% \pm 8\%$). As the pH of St. Thomas' II solution was increased further to more alkaline values, there was a sharp decline in recovery of aortic flow. In contrast to immature hearts, mature hearts were much less able to tolerate extremes of pH. All hearts treated with cardioplegic solution returned spontaneously to normal sinus rhythm within 60 seconds after reperfusion. Heart rate was depressed on reperfusion for hearts exposed to extreme acidic (pH < 5.8) and alkaline (pH > 8.3) environments, but these differences were not significant.

POSTISCHEMIC ENZYME LEAKAGE. Figure 4 shows that for mature hearts protected with hypothermia alone, where the pH of the coronary perfusate was 7.25, creatine kinase leakage during the 15-minute Langendorff reperfusion period was 181 ± 22 IU/g dry weight. When hearts were protected by hypothermia plus the standard St. Thomas'

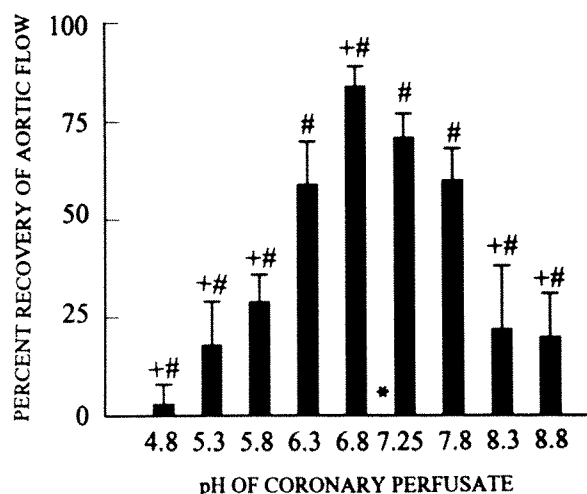


Fig 3. pH and cardioplegic protection in the mature heart: relationship between postischemic recovery of aortic flow and pH of the pre-ischemic perfusate. Closed histograms represent data from hearts protected by hypothermia plus cardioplegia. The asterisk represents data from hearts protected by hypothermia alone; there was no recovery of function. Data shown represent the mean $\pm$ the standard deviation from 6 hearts per group. (+ = $p < 0.05$, hypothermia plus cardioplegia; pH 7.8 versus modified pH; # = $p < 0.05$, hypothermia alone versus hypothermia plus cardioplegia.)

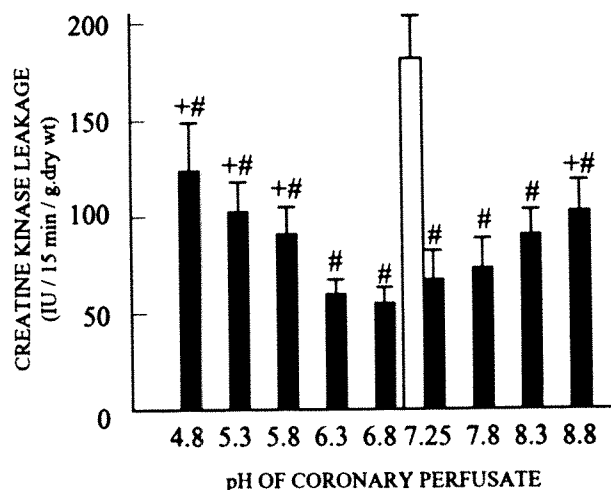


Fig 4. pH and cardioplegic protection in the mature heart: relationship between postischemic creatine kinase leakage and pH of pre-ischemic perfusate. Closed histograms represent data from hearts protected by hypothermia plus cardioplegia. The open histogram represents data from hearts protected by hypothermia alone. Data shown represent the mean $\pm$ the standard deviation from 6 hearts per group. (+ = $p < 0.05$, hypothermia plus cardioplegia; pH 7.8 versus modified pH; # = $p < 0.05$, hypothermia alone versus hypothermia plus cardioplegia.)

II solution (pH 7.8), creatine kinase leakage was reduced to 75 ± 15 IU/g dry weight. In contrast to immature hearts, a more pronounced U-shaped dose-response profile was observed for pH and creatine kinase leakage in mature hearts. As the pH of the cardioplegic solution decreased from its normal value of 7.8, there was a decline in postischemic enzyme leakage with a nadir of 55 ± 8 IU/g dry weight at a pH of 6.8. However, as the pH of the cardioplegic solution was reduced to even more acidic values, creatine kinase leakage gradually increased to 124 ± 25 IU/g dry weight at pH 4.8. Similarly, as pH was gradually made more alkaline, creatine kinase leakage progressively increased to 102 ± 16 IU/g dry weight at pH 8.8.

pH and Calcium Activity of Cardioplegic Solution

Figure 5 shows the relationship between pH and calcium activity of the cardioplegic solution. For the unmodified cardioplegic solution (pH 7.8), calcium activity was 1.07 ± 0.01 mmol/L. Titration of the solution to a more acidic or alkaline pH resulted in a bell-shaped dose-response profile for ionized calcium and hydrogen ion concentrations. The calcium ion activity at pH 4.8 and 9.3 was depressed to 0.91 ± 0.02 mmol/L and 0.84 ± 0.02 mmol/L, respectively. There were no significant changes in calcium ion activity over the pH range 6.3 to 8.3. The total (elemental) calcium content of the cardioplegic solution was 1.2 ± 0.01 mmol/L.

pH and Temperature of Coronary Perfusates

Figure 6 shows the relationship between temperature and measurement of pH for the two coronary perfusates. The

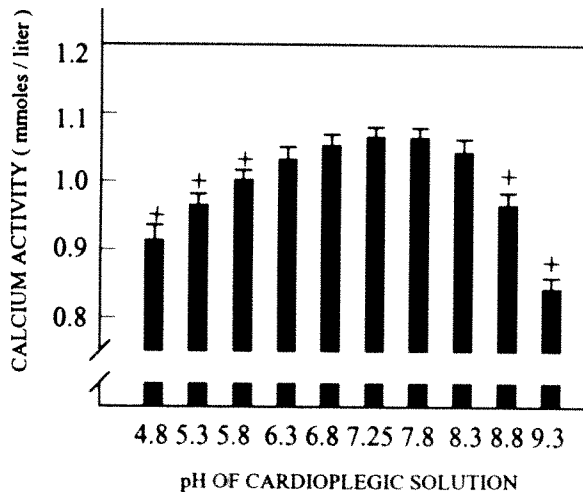


Fig 5. pH and calcium activity of the cardioplegic solution. The solid line represents the total (elemental) calcium content of the cardioplegic solution. The solid bars represent the calcium activity of the cardioplegic solution. Data shown represent the mean and the standard deviation from 8 separate determinations at each temperature. (+ = $p < 0.05$, calcium activity at pH 7.8 versus calcium activity at modified pH.)

pH of the St. Thomas' II cardioplegic solution was titrated initially to a value of 7.80 ± 0.01 at 14°C . As the temperature of the solution was progressively increased, the pH declined slightly to 7.76 ± 0.02 at 40°C ($p < 0.05$). When temperature was decreased from 14°C to 10°C , the pH of the solution was no different: 7.80 ± 0.01 versus 7.81 ± 0.01 , respectively. The pH of the Krebs-Henseleit bicarbonate buffer was 7.41 ± 0.02 at a temperature of 40°C . When the temperature was reduced, the pH of this buffer progressively declined to 7.19 ± 0.02 at 10°C ($p < 0.05$).

Comment

Our study demonstrates that improved cardioplegic protection of isolated, bicarbonate buffer-perfused immature and mature hearts subjected to conditions of hypothermic ischemia occurred at a pH of 6.8 as measured at 14°C . This improvement in myocardial protection by mild acidification of the cardioplegic solution was independent of age. The standard pH (7.8) of St. Thomas' II solution is less than optimal for protection of the ischemic immature and mature myocardium. Modification of the pH to 6.8 had no impact on the calcium activity of the cardioplegic solution. Changes in temperature had only a slight effect on the measurement of pH and were unable to account for the observed changes of pH on cardioplegic protection.

Experimental Model

Rabbits were selected for these studies because we [3-5] and others [18] have shown that the ischemic immature heart of this species is damaged by St. Thomas' II cardioplegic solution. The isolated heart model selected allows aspects of left heart function and metabolism to be effectively studied in the same preparation over a wide

range of experimental conditions with the heart subjected to a physiologic work load and temperature. In addition, this model has stable mechanical function with perfusate composition well controlled and easily exchanged within seconds. Through preliminary studies, we carefully defined the in vivo aortic pressure to which hearts were exposed and then matched the hydrostatic pressure of the isolated hearts to the level appropriate to the immature and mature rabbit [13].

The limitations of this type of perfusion system are well known. Aqueous solutions free of red cells, protein, and fatty acid are used to perfuse the coronary arteries. These factors serve to buffer blood-perfused preparations over a wide range of temperatures. In addition noncoronary collateral flow is absent. The hearts are maintained at relatively low end-diastolic values with no assessment made of their response to more stressful working conditions.

pH and Cardioplegic Protection of Immature and Mature Hearts

We have shown that in the isolated buffer-perfused immature heart there is a bell-shaped dose-response profile for the relationship between pH and recovery of aortic flow but not for postischemic creatine kinase leakage, with protection by the cardioplegic solution improved at an acidic pH during ischemia. Optimal myocardial protection with modified St. Thomas' II solution occurred at pH 6.8, which was better than with hypothermia alone (pH 7.25). The absence of a relationship between functional recovery and postischemic creatine kinase leakage for the immature heart calls into question the utility of enzyme leakage as a meaningful index of myocardial protection in the immature heart. We observed a bell-

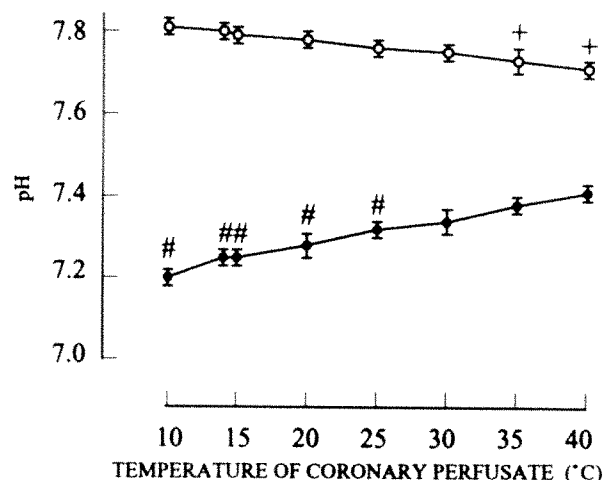


Fig 6. pH and temperature of coronary perfusates. Open circles represent data from St. Thomas' II cardioplegic solution, and closed circles represent data from Krebs-Henseleit bicarbonate buffer. Data shown represent the mean $\pm$ the standard deviation from six temperature observations in each group. (+ = $p < 0.05$, St. Thomas' II solution: pH at 14°C versus pH at other temperatures; # = $p < 0.05$, Krebs-Henseleit bicarbonate buffer: pH at 40°C versus pH at other temperatures.)

shaped dose-response curve for recovery of aortic flow and a U-shaped dose-response curve for postischemic creatine kinase leakage in the mature heart, with improved protection again occurring at a mildly acidic pH. Optimal myocardial protection of the mature heart also occurred at pH 6.8. These observations indicate that improved cardioplegic protection at a mildly acidic pH occurred regardless of the age of the heart at the time of study. The immature heart tolerated extremes of pH better than the mature heart. This may reflect the greater buffering capacity of the immature heart [19].

pH and Cardioplegic Protection

The assertion that alkaline cardioplegic solutions are best to protect the heart during ischemia was originated by Buckberg and colleagues [20-22]. To allow metabolism to continue under hypothermic conditions, poikilotherms maintain their blood pH at an alkaline value relative to the neutral point of water [8, 9]. Based on this physiological adaptation to keep pH appropriate for temperature in cold-blooded vertebrates, McConnell and co-workers [20] demonstrated that myocardial function and metabolism in warm-blooded dogs improved when blood pH was increased from 7.4 to 7.7 during hypothermic perfusion of the heart. Subsequent studies by Follette and associates [21] showed that a transient increase in the pH of blood from 7.4 to 7.8 during hypothermic reperfusion of the puppy heart after ischemia improved recovery of function. Following these studies that demonstrated the protective effect of alkaline hypothermic perfusion and reperfusion, it was assumed that alkaline conditions would also be appropriate to protect the heart during ischemia. This belief was supported in part by the fact that toxic acidic metabolites are known to be produced during ischemia [7]. Thus the potential existed for attenuating the onset and development of acidic conditions with the provision of an extracellular alkaline environment before and throughout ischemia. Based on these considerations, alkaline cardioplegic solutions were introduced into clinical use [13, 22].

Our study has demonstrated that titration of the pH of St. Thomas' II solution to mildly acidic values improved recovery of both immature and mature hearts after hypothermic ischemia. This paradoxical finding, in contrast to the studies of Buckberg and co-workers [20-22], is supported by considerable experimental evidence. For example, in studies on the hypoxic adult rat papillary muscle, functional recovery was increased in muscle bathed in acidic conditions during hypoxia [23]. Further support for the creation of an acidic environment during ischemia was provided by Rouslin and associates [24]. They determined that an increased hydrogen ion concentration inhibited the net rate of tissue adenosine triphosphate depletion in an autolytic model of cardiac ischemia, resulting in better preservation of high-energy phosphate stores. Poole-Wilson [25] has shown that a mild intracellular acidosis during hypoxia inhibits adverse calcium fluxes and calcium loading of mitochondria after reoxygenation. These events favor improved functional recovery. In addition, Janke and colleagues [26] demonstrated that mature

hearts can be protected against isoproterenol-induced calcium overload by decreasing arterial blood pH to counterbalance the adverse effect of calcium uptake.

To our knowledge, there have been no studies on pH and cardioplegic protection of the ischemic immature myocardium. However, the impact of the pH of the cardioplegic solution on myocardial protection in the adult has been investigated previously. Bernard and associates [27] studied the effect of cardioplegic solutions buffered to pH 7.0, 7.4, and 7.7 on intracellular pH as measured by phosphorus 31 nuclear magnetic resonance spectroscopy and on functional recovery as measured by aortic flow after 2 hours of global ischemia at 15°C in the rat. Hearts protected with the cardioplegic solution buffered to pH 7.0 were characterized by better preservation of adenosine triphosphate levels throughout ischemia and reperfusion and an improved rate of restoration of aortic flow during reperfusion in comparison with the alkaline cardioplegic solutions. In studies of cardioplegic solutions and postischemic function in the dog, Nugent and co-authors [28] demonstrated that alkaline cardioplegic solutions depressed left ventricular function and metabolism more than neutral or acidic cardioplegic solutions.

Mechanisms of Acidic Protection

There are a number of potential mechanisms that may account for the effects we described. Extracellular acidosis may be exerting a protective effect on the ischemic myocardium through a limitation of intracellular calcium accumulation. Intracellular calcium overload can severely limit postischemic recovery of function. It has been proposed that during ischemia the late fall in intracellular pH inhibits sodium-calcium exchange [29, 30]. Assuming a reduction in extracellular pH at the onset of and throughout ischemia would result in a corresponding reduction in intracellular pH, then acidic conditions might be expected to inhibit intracellular sodium-dependent calcium influx. In addition, an increase in the extracellular concentration of protons may also limit sodium influx during ischemia through the sodium-hydrogen exchanger. This inhibition would limit calcium influx by decreasing intracellular sodium accumulation through this exchanger [31]. Ischemic acidosis is known to result from the retention of protons from glycolytic turnover, the accumulation of carbon dioxide, and eventually the breakdown of adenosine triphosphate. These processes are all injurious to the myocardium. The provision of an acidic environment immediately before and throughout ischemia may act to slow these changes, thus preserving cell viability.

pH and Calcium Activity of the Cardioplegic Solution

The existing calcium content of standard St. Thomas' II solution also plays a role in its less than optimal protection of both immature [6] and mature [32] hearts under conditions of clinically relevant hypothermia. We have shown that over the pH range of 6.3 to 8.3, where the pH-modified cardioplegic solution exerted an increased protection compared with the unmodified cardioplegic solution (pH 7.8), the calcium activity of the solution was unchanged. Thus pH had no impact on the calcium

content of the cardioplegic solution that could have altered its ability to protect the ischemic myocardium.

Temperature and pH of the Cardioplegic Solution

The pH of St. Thomas' II cardioplegic solution changed only 0.05 units over the temperature range 10° to 40°C. This indicated that there was no change in the pH of the solution with temperature large enough to have an impact on myocardial protection. The dose-response profile for pH, therefore, was not shifted by temperature. This observation shows clearly that St. Thomas' II cardioplegic solution, which is a bicarbonate-containing solution, is a poor buffer when used under hypothermic conditions. Its poor buffering capacity can be anticipated, as its pH does not parallel the change in the value for the neutrality point of water (pN) during progressive cooling. We emphasize that the choice of a given buffer to be included in a crystalloid cardioplegic solution should be dependent on its temperature coefficient.

The pH of St. Thomas' II solution is mildly alkaline at 7.8. We know of no studies that determine whether myocardial protection with St. Thomas' II solution is optimal at this alkaline pH. The value of 7.8 was selected on the basis of reports [8, 9] suggesting that a mildly alkaline solution was desirable in view of the rise in pH of blood in vitro that occurs on cooling [33]. This effect does not occur with St. Thomas' II cardioplegia, which is an aqueous solution, as cooling produced very little change in pH [20-22]. Thus we are unable to reconcile fully our results for the observed protective effect of an acidic aqueous cardioplegic solution with those of Buckberg, who has advocated the use of alkaline blood cardioplegic solutions on the basis of pH changes with temperature.

Temperature and pH of Bicarbonate Buffer

Temperature exerts a strong influence on the acid-base status of individual coronary perfusates. The acid-base status of the blood in vitro varies with temperature because of changes in the dissociation of weak acids, particularly carbonic acid, and proteins as well as the change in the solubility of carbon dioxide. Siggard-Andersen [12] has shown that a decrease in the temperature of blood at a constant carbon dioxide tension results in an increase in pH. However, for a simple bicarbonate buffer as used in our study, a decrease in temperature at a constant carbon dioxide tension results in a decrease in pH. This relationship can be predicted from the van't Hoff and Henderson-Hasselbach equations [12]. We confirmed this in the present study.

Temperature and Measurement of Perfusate pH

The variation in pH with temperature can lead to difficulties in pH measurement in physiological situations with hypothermia. In our study, the pH of the coronary perfusates was determined at 14°C, a temperature commonly achieved during intraoperative myocardial protection. The variation in pH of an aqueous cardioplegic solution such as St. Thomas' II over the temperature change from 10° to 40°C was small. However, the impact of hypothermia on the measurement of pH of blood

would be much greater [33]. Ream and colleagues [34] have advocated that the measurement of pH at hypothermic temperature be without correction for the known changes in pH with temperature. The correction of pH with respect to temperature in assessing the acid-base status of blood perfusates requires further study.

Conclusion

In conclusion, we have shown that cardioplegic protection of the ischemic rabbit heart is improved under mildly acidic conditions. This effect is independent of the age of the heart at the time of study. It is apparent that the existing pH of St. Thomas' II cardioplegic solution is less than optimal to protect the ischemic immature myocardium in this model. The underlying mechanism responsible for this effect remains to be determined but places into question the dogma that alkaline cardioplegic solutions are best to protect the ischemic heart. Our studies relate only to the protection of isolated buffer-perfused hearts and not to in vivo blood-perfused preparations. Caution must also be applied in extrapolating these results to the clinical situation, as the studies described here relate only to the normal, healthy heart and do not reflect the impact of an underlying disease state on tolerance to ischemia and protection with cardioplegic solutions.

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Delayed Myocardial Laceration After Intrapericardial Pneumonectomy

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Curative resection for large central bronchogenic tumors may require radical or intrapericardial pneumonectomy. Myocardial herniation through the pericardial defect is a rare early postoperative complication. Prevention of cardiac herniation and subsequent hemodynamic compromise is always necessary after intrapericardial pneumonectomy.

(*Ann Thorac Surg* 1993;55:756-7)

A 72-year-old man was found to have a left hilar squamous cell bronchogenic carcinoma. Resectability was assessed by bronchoscopy, computed tomographic scan of the thorax, and mediastinoscopy.

At thoracotomy the tumor was centrally located and attached to the left pulmonary artery at its origin with the main pulmonary trunk. The pericardium was opened longitudinally anterior to the phrenic nerve from the hilum to within 3 cm of the diaphragm to facilitate ligation of the hilar vessels. The left pulmonary artery was clamped at its junction with the main pulmonary artery, divided, and suture ligated. The pulmonary veins were stapled flush with the left atrium. After completion of the resection, the pericardial defect, which measured approximately 8 cm by 4 cm, was not repaired. The mediastinum was balanced by removing 1 L of air through a red rubber catheter, which was then removed. The patient was extubated in the operating room (Fig 1).

The first postoperative day was complicated by sinus bradycardia. An electrocardiogram revealed low voltage in all leads, flipped T waves in lead III and the precordial leads, and nonspecific ST changes. Serum creatinine kinase level was elevated but the MB fraction was within normal limits.

On the second postoperative day hypovolemic shock developed (Fig 2). After fluid resuscitation a left thoracotomy was performed. The chest was evacuated of blood and clot. All the hilar sutures were secure. The heart had herniated from the pericardium, the apex of the left ventricle was edematous and hypokinetic, and a distal branch of the left anterior descending artery in the center of the injured myocardium was bleeding. The vessel was oversewn and the remainder of the pericardium was

divided to the diaphragm to prevent incarceration of the left ventricle.

The patient left the hospital 10 days after his second operation having followed a smooth postoperative course.

Comment

Cardiac herniation after intrapericardial pneumonectomy is a rarely reported complication associated in the literature with a 50% mortality [1, 2]. Reported cases have occurred with pericardial defects of any size [2, 3], and even when partial or complete closure of the pericardium is performed at the time of the initial operation [4].

Reported cases have attributed the pathophysiologic result of cardiac herniation to occlusion of the great vessels. Hemodynamic compromise occurs after herniation through either right-sided or left-sided pericardial defects, but superior vena caval syndrome more commonly is observed in association with right-sided defects [4]. A recent review of 50 cases [1] classifies cardiac herniation and its hemodynamic effects by anatomic side: right-sided herniations cause predominantly a diminished

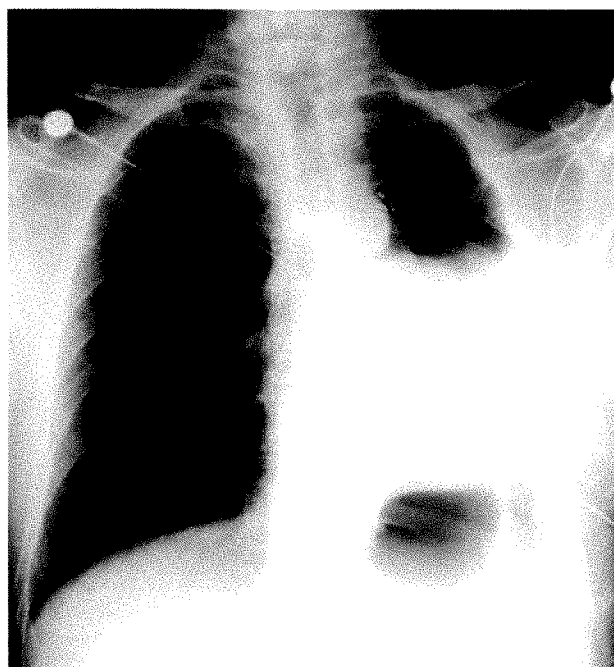


Fig 1. The immediate postoperative chest roentgenogram demonstrated a high left hemidiaphragm and a central mediastinum.

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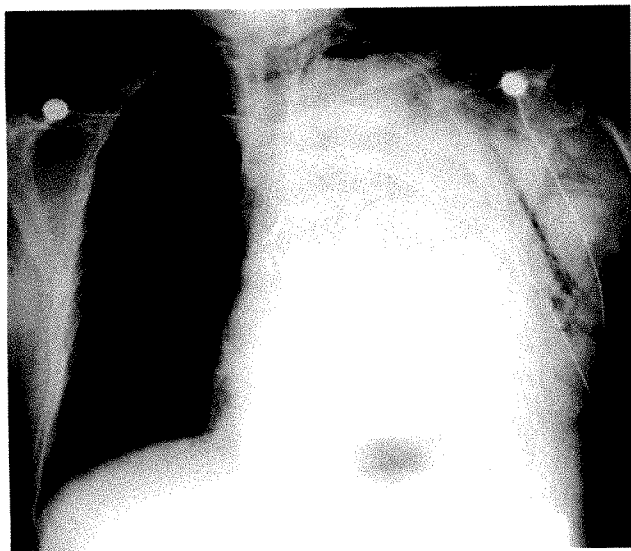


Fig 2. Chest roentgenogram on second postoperative day showed complete opacification of the left hemithorax.

cardiac output by obstruction of the venous return and left-sided herniation more often produces myocardial ischemic and dysrhythmias from diminished coronary blood flow caused by compression of the coronary arteries by the edges of the pericardial defect [5].

In this case, the heart likely herniated from the pericardium in the immediate postoperative period, without any serious hemodynamic effect. Compression of the apex of the left ventricle by the pericardial edges produced myocardial edema and localized ischemia, as evidenced by the electrocardiographic changes. The myocardium and an epicardial artery were lacerated by the anterior border of the resected fifth rib, producing a massive hemothorax.

Small defects adjacent to the pulmonary hila can be closed primarily but are usually left open because cardiac herniation complicated by either torsion or strangulation is very infrequent and closure under tension risks causing

tamponade. When the defect in the pericardium is large and cardiac herniation is possible, two options are available. On the left side, the pericardium can be opened down to the diaphragm [6]. This does not prevent herniation, but cardiac strangulation or infarction is unlikely. On the right side, the defect must be closed. This can be accomplished either by suturing the cut edges of the pericardium to the epicardium [7] or by patching the defect with parietal pleura [8] or fascia lata [9]. Dacron has been used [3]; however, septic complications have thus far limited its use.

Our approach, based on our experience, is to repair all large pericardial defects, regardless of side, after intrapericardial pneumonectomy. We now use Vicryl mesh to repair such defects. This material prevents herniation but is absorbable, thereby eliminating foreign material from the postpneumonectomy space. Efforts should be directed toward preventing cardiac herniation. Vigilant observation must be maintained to assist in early detection of this uncommon complication.

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Long-Term Follow-up and Resection of a Postoperative False Aortic Aneurysm

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This report describes the course and operative findings in a 66-year-old man with a densely calcified false aneurysm of his ascending aorta 19 years after replacement of a severely stenosed bicuspid aortic valve with a McGovern-Chromie prosthesis. This report emphasizes the need to consider this possibility, even in patients with a very remote prior operation.

(*Ann Thorac Surg* 1993;55:758-9)

A 47-year-old man underwent replacement of a densely calcified and severely stenotic bicuspid aortic valve with a McGovern-Chromie prosthesis in May of 1969. A 1-cm sternal dehiscence developed 2 weeks later, which was closed with stainless steel and chromic cat gut suture. He became febrile 4 weeks later, at which time six blood cultures all grew *Staphylococcus epidermidis*. His fever promptly subsided after treatment with vancomycin, and his blood cultures remained sterile thereafter.

During the 19 ensuing years he worked full time as a medical records administrator and remained physically active without cardiovascular symptoms. He was maintained on warfarin sodium and subacute bacterial endocarditis prophylaxis when indicated. Anterior mediastinal calcification was noted on a routine follow-up lateral chest roentgenogram, and review of previous films revealed these findings to have been present but less prominent during the preceding 8 years. Computed tomographic scan revealed a large false aneurysm of the ascending aorta arising in the region of the previous aortotomy and extending to the sternum (Fig 1). The extent of the false aneurysm was further defined by aortography (Fig 2). The McGovern-Chromie prosthesis continued to function normally by clinical, echocardiographic, and Doppler assessment.

Operation was performed in October 1988 using cardiopulmonary bypass with cannulation of the femoral artery and vena cava by the femoral vein. The patient's temperature was lowered to 22°C. When the sternum was opened the aneurysm was entered, necessitating a brief period of circulatory arrest until the aorta had been

cross-clamped. The aneurysm measured 4.5 cm, was calcified, and involved the aortic suture line. It was densely adherent to the undersurface of the sternum. The 19-year-old McGovern-Chromie valve appeared normal and was not replaced in view of the additional difficult dissection and prolonged perfusion time that would be required. The ascending aorta was replaced with a 30-cm woven Dacron graft. The patient's postoperative course was uneventful, and he was asymptomatic at his most recent evaluation in October 1991.

Comment

False aneurysms have been reported to complicate aortotomy, aortic cross-clamping, cannulation, needle insertion sites, and aortic suture lines. In a series of 1,000 coronary artery bypass graft procedures, pseudoaneurysm accounted for 3% of the late deaths [1]. In a recent report of 31 cases of pseudoaneurysm, formation infection was implicated in 18 cases [2]. Pseudoaneurysm formation has also been reported as a complication of cardiac transplantation in association with infection.

Computed tomographic scan has proven to be invaluable as a guide to surgical management, although magnetic resonance imaging has also been useful [3, 4]. Precise localization of the pseudoaneurysm reported here resulted in the initiation of cardiopulmonary bypass from the groin, which provided an additional margin of safety for the dissection.

The McGovern-Chromie sutureless valve used in the

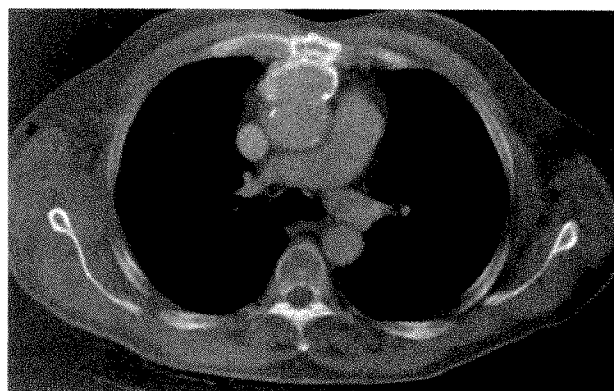


Fig 1. Noncontrast computed tomogram of the chest showing the calcified pseudoaneurysm of the ascending aorta.

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The views presented are those of the authors and do not reflect the official views of the US Navy or the Department of Defense.

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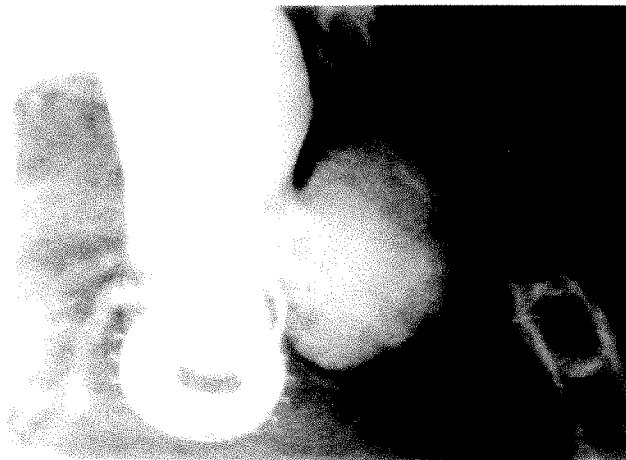


Fig 2. Aortogram showing the McGovern-Chromie aortic valve with the pseudoaneurysm arising in the ascending aorta adjacent to the sternum.

1960s because of its rapid insertion was subsequently abandoned because of a relatively high incidence of thromboembolic complications and perivalvular leaks.

This case, however, demonstrates that it is possible for the McGovern-Chromie sutureless prosthesis to function normally without complications for a period of more than 22 years.

A previously reported postoperative false aneurysm was recognized during life 9 years after operation [2]. This case indicates that a much longer survival is possible and that this diagnosis should be considered in postoperative patients long after this time period, especially when there has been perioperative infection.

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Traumatic Sinus of Valsalva Fistula and Aortic Valve Rupture

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A rare case of nonpenetrating trauma-induced fistula from the right sinus of Valsalva to the right atrium and aortic cusp disruption is reported. The trauma occurred 2½ years previously. The fistula was closed with a Dacron patch, and the cusp tear was sutured.

(Ann Thorac Surg 1993;55:760-1)

Traumatic aorto-right atrial fistula after blunt chest trauma is rarely reported. An unusually long delay between the trauma and the development of symptoms can occur; eventually cardiac insufficiency may develop. Therefore it is important to keep in mind the possibility of a complex cardiac lesion: sinus of Valsalva fistula and aortic valve regurgitation.

A 34-year-old railway worker had driven into an oncoming car at a junction 2½ years previously. Chest contusion was diagnosed at the local hospital. Previously he had been robust according to the yearly checkups at the railway occupational medicine department. Three months after the accident he underwent his yearly checkup and a new diastolic murmur was noted. He was referred to a cardiologist, who diagnosed mild aortic insufficiency. Eighteen months later he began to notice a reduction in exercise capacity. Then he noticed marked dyspnea after climbing the steps to the control tower at work. He went back to the cardiologist, who sent him for angiography. At that time his blood pressure was recorded at 125/30 mm Hg. He did not have any overt signs of cardiac failure. An early systolic murmur was heard over the second intercostal space at the right sternal border, and a diastolic murmur was heard over the left sternal border. Electrocardiogram showed bilateral ventricular enlargement and complete right bundle-branch block. Echocardiography done at this time showed enlargement of the left ventricle with an end-diastolic diameter of 71 mm. The right heart chambers were considered normal in size. Color Doppler echocardiography showed mild aortic valve regurgitation. Cardiac catheterization disclosed raised pressure in the right heart: mean atrial pressure was 8 mm Hg; right ventricular pressure was 30/7 mm Hg.

Left ventricular end-diastolic pressure was increased to 20 mm Hg. The oxygen saturation in the right atrium and ventricle was 80%. Aortic angiography revealed a communication between the right coronary sinus and the right atrium (Fig 1). A sinus of Valsalva-right atrial fistula with left to right shunt of 45% of the pulmonary flow was diagnosed.

He was then referred to our hospital for operation. The patient was tall and thin and not in distress (New York Heart Association class II). A continuous murmur (grade 3) was heard along the left sternal border. Color Doppler examination confirmed the diagnosis of sinus of Valsalva fistula, and a jet of aortic insufficiency was also seen.

At operation a rough fistula tract extending from below the right coronary ostium to the septal wall of the right



Fig 1. Aortic angiography revealed a communication between the right coronary sinus and the right atrium.

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atrium above the septal cusp of the tricuspid valve was closed with a pericardial patch. On inspection of the aortic valve, several small perforations near the commissure of the right and left coronary cusps were seen. These were closed with Teflon sponge-backed sutures. The patient made an uneventful postoperative recovery and remained in sinus rhythm. Postoperative color Doppler examination confirmed a good result with no valve dysfunction and no shunt.

Comment

This case of delayed development of traumatic sinus of Valsalva fistula supports the hypothesis on the pathogenesis put forward in previous reports [1, 2]. Because of the delay between the trauma and operation it is almost impossible to differentiate from rupture of congenital aneurysm of the sinus of Valsalva. The traumatic tear in the aortic wall dissected into the root, and the wall of the right atrium was subjected to the eroding pressure. In a previous report the delay in this scenario was 18 months [2]. In this report the delay was 2½ years. When the fistula eventually occurs, the rapidity of deterioration in the patient's cardiac status depends on the shunt developed. In our patient a shunt of 45% of the pulmonary circulation was present.

Interesting features of this case are the unusual con-

comitant occurrence of aortic insufficiency, which obscured the diagnosis, and the long delay between the trauma and the fistula rupture. The delay may be explained by the low mean pressure in the aorta. In the only other reported case of a patient with both aortic regurgitation and a sinus of Valsalva-right atrial fistula after nonpenetrating chest injury, the symptoms were attributed to aortic insufficiency [3]. As in our case the signs of aortic valve rupture masked those of the sinus of Valsalva-right atrial fistula, and the presence of the fistula was only detected by preoperative cardiac catheterization.

According to a recent report [4] accurate diagnosis of sinus of Valsalva fistula can be made with color Doppler echocardiograms. Cardiac catheterization and aortography are optional diagnostic procedures.

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Successful Repair of Combined Ventricular Septal Rupture and Free Wall Rupture

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The successful surgical repair of combined ventricular septal perforation and free wall rupture (double rupture) after inferior myocardial infarction is reported. Extensive inferior wall infarctectomy was performed, and both defects were closed with a prosthetic patch, using a modification of the technique developed by Daggett. The patient was alive and well 1 year after operation.

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We report a case of combined free wall rupture and ventricular septal perforation (double rupture) after inferior myocardial infarction in which surgical repair was successful.

A 63-year-old man was diagnosed as having a ventricular septal perforation, a left ventricular aneurysm, and cardiac failure after an inferior myocardial infarction. He was transferred to our hospital for surgical repair 17 days after the infarction. After admission, a Swan-Ganz catheter was inserted, and the right atrial pressure, pulmonary artery pressure, and pulmonary capillary wedge pressure were 10 mm Hg, 51/16(36) mm Hg, and 20 mm Hg, respectively. The pulmonary to systemic flow ratio was calculated to be 3.3.

Two days after admission, rapid hemodynamic deterioration was observed despite the administration of inotropic drugs and diuretics and institution of intraaortic balloon pump support. Urgent cardiac catheterization was performed, and left ventricular angiography showed a large posterior-inferior aneurysm, with a defect in the inferior ventricular septum, leading to opacification of the right ventricle and pulmonary artery. Coronary angiography showed 99% occlusion of right coronary artery segment 1 and 75% stenosis of left circumflex artery segment 14.

An operation was performed 19 days after the infarction. A median sternotomy was performed, and a substantial hemopericardium was noted. After systemic heparinization, the ascending aorta was cannulated for arterial perfusion, and the superior and inferior venae cavae were cannulated through the right atrial wall to institute cardiopulmonary bypass. A left ventricular vent

was inserted from the right upper pulmonary vein through the left atrium. Rectal temperature was reduced to 26°C. After aortic cross-clamping, crystalloid cardioplegia was instilled into the aortic root, and the heart was cooled topically. Then the heart was dislocated up out of the pericardial sac and examined. Thinning of the ventricular wall in the area of the infarction was observed around the 4PD segment of the coronary artery, and a fibrin clot was adherent to the infarcted area. This region was believed to be the site of the left ventricular free wall rupture. The region was posterior-inferior and measured approximately 4 cm in diameter. The margins of the infarcted myocardium were determined carefully, and the lesion was excised elliptically. The ventricular septal perforation was 1.5 × 2 cm and was located on the apex side of the infarcted free left ventricular wall (Fig 1).

Ticron (American Cyanamid Co, Wayne, NJ) 2-0 interrupted mattress sutures, buttressed with Teflon felt pledgets, were brought through from the right ventricular side of the septal margin circumferentially, a Dacron patch was placed on the left ventricular side of the septal perforation, and sutures were tied. The interrupted mattress sutures in the margin of the septal perforation of the free wall were passed from the patch side to the epicardial surface and buttressed with a Teflon felt strip on the epicardial surface but were not tied at this point (Fig 2). The left ventricular free wall was reconstructed with a Teflon felt patch. Mattress sutures of 2-0 Ticron, buttressed with Teflon felt pledgets, were placed circumferentially from the endocardial surface around the margin of the left ventricular free wall, except at the edge adjacent to the septal perforation, where untied felt strip-reinforced sutures for septal perforation patch closure were used. The patch was trimmed, and the sutures were brought through from the endocardial side to slide the patch down to the epicardial surface of the ventricle (Fig 3). Concomitant revascularization was not performed. The patient was weaned from cardiopulmonary bypass with the aid of an intraaortic balloon pump. The patient was discharged and was classified in New York Heart Association functional class I after a 1-year follow-up.

Comment

As complications of myocardial infarction, clinical case reports of double rupture are rare [1-7], and cases of successful surgical repair are even more rare [1, 3, 4, 6, 7]. Moreover, among the cases reviewed, survivors included only patients with anterior wall infarction, probably in

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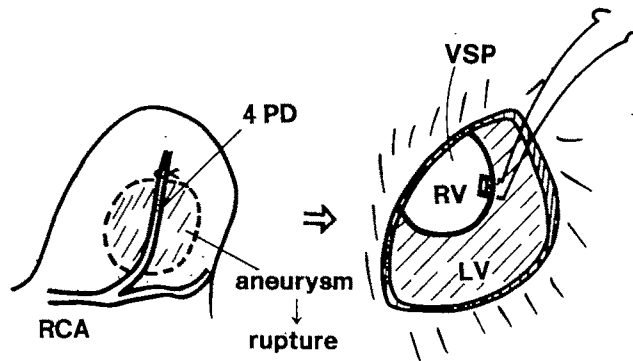


Fig 1. Schematic illustration of inferoposterior aspect of heart and the view of excised aneurysm. (LV = left ventricle; RCA = right coronary artery; RV = right ventricle; VSP = ventricular septal perforation; 4PD = segment 4PD of the right coronary artery.)

part due to the anatomic difficulties involved in reconstruction. The factors that contributed to the favorable result in this case include the following: (1) The free wall rupture was not a blowout, but a hemorrhagic dissecting type. (2) Cardiac rupture was delayed, occurring 18 days after infarction. The subacute phase of infarction is a favorable time for reconstruction. The likelihood of a second rupture or failure of the reconstruction is reduced, because the margins of the area of infarction can be determined with greater certainty and myocardial fibrosis and reduced tissue friability allow sutures to be placed more securely. (3) Even after ventricular septal perforation, the patient remained hemodynamically stable until the free wall ruptured. Thus a successful outcome, even when septal perforation has occurred, depends upon careful clinical assessment. Clinicians need to be especially alert to newly evolving or persistent chest pain [1-3] and signs of cardiac tamponade before electromechanical dissociation or circulatory collapse develop. Interestingly, the diagnosis of free wall rupture was not made preoperatively in any reported case, including ours.

Surgical procedures, especially the reconstruction technique, can be ascribed to isolated ventricular septal perforation reconstruction theoretically. Therefore, our method was mostly based on those described by Daggett

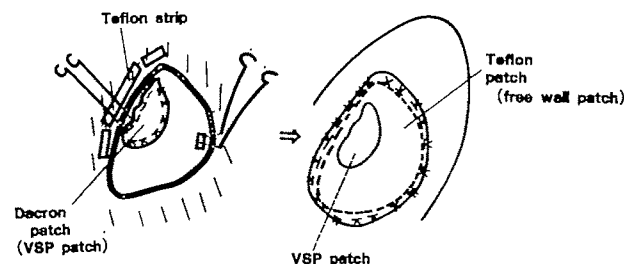


Fig 2. Schematic illustration of the reconstruction of ventricular septal perforation and free wall defect. (VSP = ventricular septal perforation.)

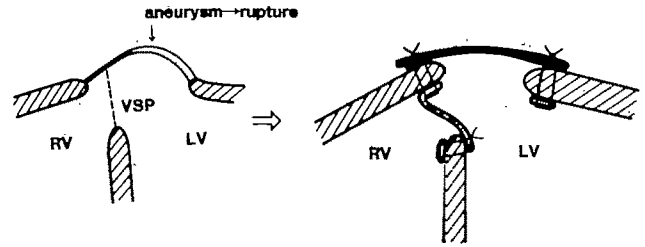


Fig 3. Patch reconstruction of ventricular septal perforation and ruptured free wall aneurysm. (LV = left ventricle; RV = right ventricle; VSP = ventricular septal perforation.)

[8]. The main technical factors to consider in the repair of double rupture after inferior infarction include the following: (1) Repair of the septal defect is performed through the left ventricular incision. (2) Complete resection of the infarcted inferoposterior left ventricular wall is essential to prevent delayed rupture. (3) Both the septal and free wall defect are closed by prosthetic patch reconstruction from the left ventricular and epicardial side, respectively, to restore anatomic continuity without tension. We have adopted a noneverted method, reinforced by either felt pledgets or strips to prevent cracking and leakage.

In conclusion, patient salvage after combined ventricular septal perforation and left ventricular free wall rupture secondary to inferior myocardial infarction was achieved; such salvage can be achieved if surgical repair by techniques established for inferoposterior ventricular septal perforation [8] is performed before circulatory collapse or vital organ failure occurs.

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Ventricular Septal Defect Creation for Relief of Tunnel Subvalvular Aortic Stenosis

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In infants, the management of severe tunnel subvalvular aortic stenosis associated with hypoplastic aortic annulus remains a major surgical challenge. We report a case of such lesion treated by rerouting the systemic blood flow through a created subpulmonary ventricular septal defect

toward the right ventricular outflow tract and the pulmonary valve. This technique provided complete relief of the left ventricular outflow tract obstruction without the implantation of a systemic prosthetic valve.

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Tunnel subvalvular aortic stenosis (TSVAS) is a circumferential zone of stenotic fibrosis involving the left ventricular outflow tract (LVOT). In most severe cases, the aortic annulus is often hypoplastic. Surgical management of such a form remains a technical challenge, including enlargement of the aortic annulus [1] or palliative bypass [2]. These techniques require prosthetic aortic valve implantation and often fail to provide satisfactory results or appear unsuitable for use in infants. To overcome these drawbacks we elected to perform an operation precluding the use of a left-sided prosthetic valve.

A hypotrophic girl, aged 11 months and weighing 5,780 g, was admitted with a diagnosis of TSVAS associated with aortic annulus hypoplasia. Auscultation revealed a grade 4/6 systolic murmur, and the chest roentgenogram showed a cardiomegaly associated with pulmonary edema. Color-coded Doppler echocardiographic study revealed a severe TSVAS (subaortic diameter, 4 mm) with a hypoplastic aortic annulus (annulus diameter, 5 mm). Septal thickness was 13 mm. Fractional shortening was 0.34. Left ventricle–ascending aorta gradient was 135 mm Hg. Congenital mitral valve abnormalities were noted, including minimal insufficiency and suspicion of a supra-ventricular ring. Emergency surgical treatment without angiographic evaluation was required due to the life-threatening clinical condition. Because of the patient's age and the association of an evolutive hepatic disease (primary sclerosing cholangitis), we did not implant a prosthetic systemic valve.

The operation was performed under standard cardiopulmonary bypass, and myocardial protection was obtained using cold crystalloid cardioplegia. The ascending aorta and pulmonary trunk up to the bifurcation were dissected and controlled. A vertical incision was made on the anterior surface of the aorta (Fig 1) to confirm the LVOT obstruction at both aortic and subaortic levels and

to provide adequate exposure; this incision was not a part of the future repair. The mitral valve was exposed through a left atriotomy. Its examination showed no evidence of supra-ventricular stenosis, and no further approach was performed. Through a transverse infundibulotomy, a large ventricular septal defect (VSD) was created in the infundibular septum away from the medial papillary muscle to preserve the conductive pathways (Fig 2). The initial septal incision was safely performed with the aid of a Hegar dilator placed in the LVOT. Enlargement of the VSD was obtained by predominantly leftward myectomy under direct vision (VSD diameter, 12 mm). The VSD was then baffled to the pulmonary valve using a double velour Dacron patch lined with preserved heterologous pericardium (Fig 3). The main pulmonary artery was then divided. A second vertical aortotomy was performed in the left lateral aspect of the ascending aorta. The proximal main pulmonary artery was obliquely trimmed and anastomosed end-to-side to the aorta using absorbable running suture. Finally, the right ventricular outflow tract was reconstructed using a 14-mm porcine-valved Dacron conduit (Fig 4).

The patient was easily weaned from cardiopulmonary bypass in sinus rhythm with moderate inotropic support. Intraoperative data showed immediate relief of LVOT obstruction with a residual gradient of 30 mm Hg.

The patient's postoperative hemodynamic condition improved and color-coded Doppler echocardiographic examination showed an excellent patency of the created LVOT with a left ventricle–ascending aorta gradient of 20 mm Hg at the septal level. No neo-aortic regurgitation was noted. Right heart function was preserved despite the loss of the outlet portion of the right ventricle. The patient could be extubated on the 15th postoperative day.

Two days later, assisted ventilation was again required for hemodynamic degradation with pulmonary edema. A new Doppler echocardiographic study showed persistence of excellent LVOT patency. However, severe mitral valve dysfunction (insufficiency and stenosis) was noted. Dramatic improvement of the patient's postoperative cardiac output probably worsened the transmitral valve gradient. Reoperation revealed a parachute-like mitral

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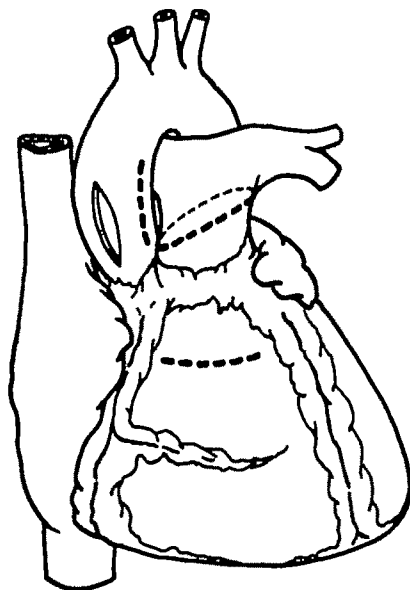


Fig 1. Incisions needed for the repair including anterior and left-sided vertical aortotomies, pulmonary trunk division, and right transverse infundibulotomy.

valve. Complex mitral valve repair was obtained for correction of stenosis but could not be technically achieved against insufficiency. Mitral valve replacement was performed with difficulty (mitral annulus diameter, 14 mm), and the patient could not be weaned from cardiopulmonary bypass. Autopsy showed that the mitral valve dysfunction was unrelated to the LVOT repair.

Comment

One of the most important aspects in the surgical management of TSVAS is to precisely determine the size of the

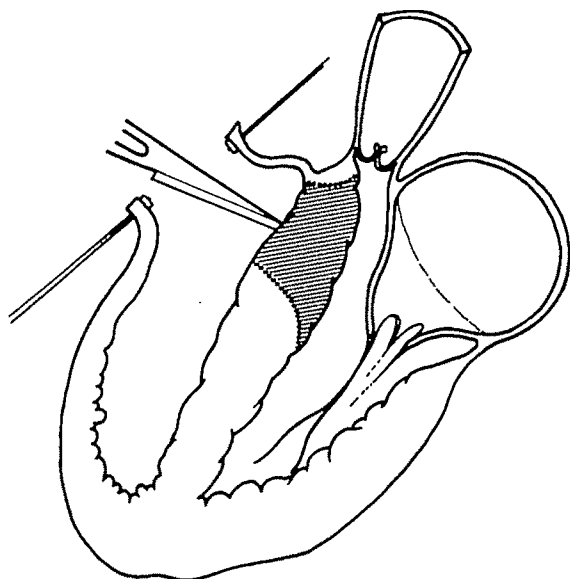


Fig 2. Creation of the ventricular septal defect (shaded area) in the infundibular septum through the right infundibulotomy.

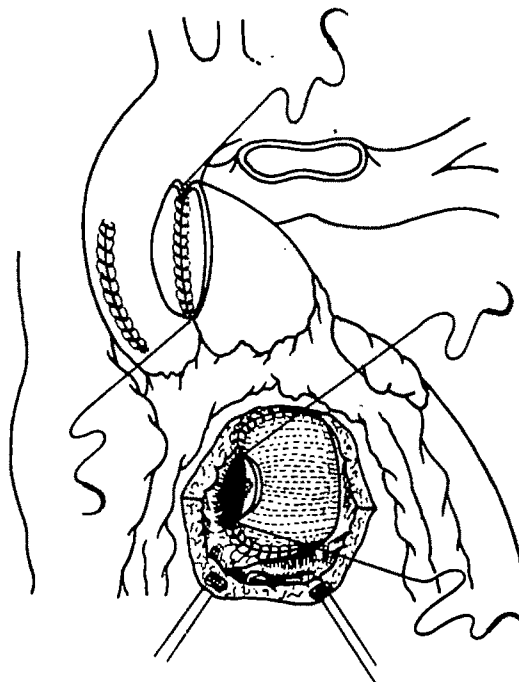


Fig 3. Completion of the new left ventricular outflow tract by tunnelization of the ventricular septal defect followed by pulmonary artery to ascending aorta anastomosis.

aortic annulus [3]. In the presence of a normal-sized aortic annulus, several effective techniques have been described to obtain complete relief of the LVOT obstruction with preservation of the native aortic valve [3, 4].

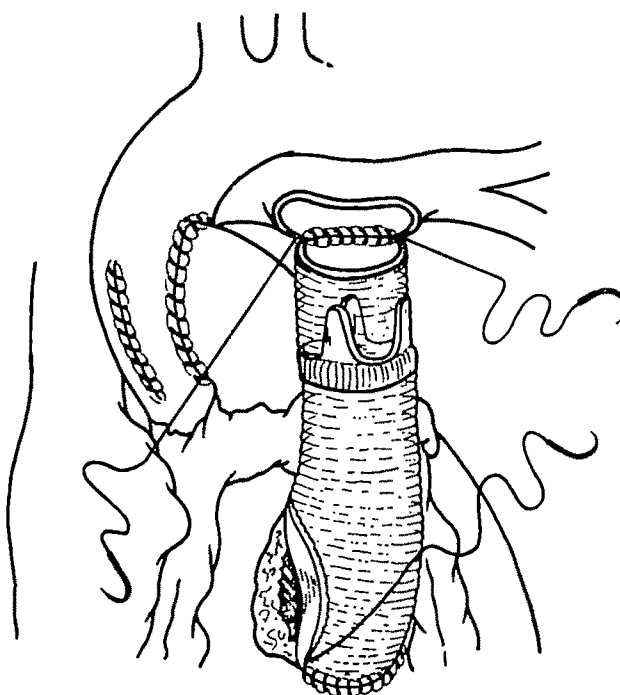


Fig 4. Right ventricular outflow tract reconstruction using a 14-mm porcine-valved Dacron conduit.

Conversely, in the presence of a hypoplastic aortic annulus, almost all reported technical solutions require a prosthetic aortic valve, which is associated, especially in children, with valve-related complications. In infants, the procedure described by Konno and associates [1] often fails to allow implantation of an available sized prosthetic valve. Nevertheless, such a procedure has been successfully employed in a neonate using a 15-mm pericardial valve, but a redo aortic valve replacement was necessary 2 years later [5]. A modification of the Konno procedure, using cryopreserved allografts for aortic root replacement and aortoventriculoplasty, has been successfully employed in infants [6]. The long-term fate of such reconstructions still needs to be evaluated, especially regarding allograft calcification and growth potential. Moreover, availability of size-matched allografts is not easy to obtain when the patient requires an urgent treatment. Left ventricle-aortic conduit interposition is effective to obtain ventricular decompression, but it is associated with high early and late mortality and morbidity, especially in infants less than 2 years of age [2]. Moreover, extracardiac conduit repair remains a palliative procedure and potentially requires a reintervention.

The inconsistency of these results led us to create the operation described in this report. Similar procedures have been employed successfully in the presence of a preexisting VSD [7]. In our patient, it was necessary to create a subpulmonary VSD, which may safely be performed as demonstrated in a case of transposition of the great arteries with intact ventricular septum and LVOT obstruction [8]. Rare complications of the septal incision (mainly complete heart block) could be potential drawbacks [3, 4]. Based on the observations in congenitally preexistent VSD [7], one might anticipate an intact LVOT growth potential, particularly at the septal level.

In summary, the technique we described reaches the

two main goals in the surgical management of this malformation: (1) at the subvalvular level, to obtain complete relief of the LVOT obstruction; and (2) at the valvular level, to preclude the use of a left-sided prosthetic valve. Obviously, the technical feasibility in infants and the efficacy of this combination of two-level procedures are the sole conclusions that could be made. The real importance of this procedure is not yet determined. However, it may be a useful technical alternative in selected cases of TSVAS.

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Intraoperative Transthoracic Ultrasonographic Localization of Occult Lung Lesions

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During video-assisted thoracoscopic operations, identification of small peripheral lung nodules can be challenging. We report the use of intraoperative intrathoracic ultrasonography for localization of lung tumors before resection in 2 patients.

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Over the last year, we have seen an explosion of new instrumentation for endoscopic surgery. Video-assisted thoracoscopic surgery has become an important addition to the variety of techniques by which thoracic surgeons are capable of handling diverse intrathoracic problems [1-3]. Wedge resection of peripheral lung lesions, whether for diagnostic or therapeutic purposes, has become one of the most common indications for video-assisted thoracic surgery. Localization of the lung lesion, however, has been one of the major limitations for application of thoracoscopic techniques in the removal of such lesions. Recently Mack and associates [4] proposed the use of computed tomography-guided needle localization, a technique previously used to facilitate localization of nonpalpable breast lesions, as a method that would allow thoracic surgeons to identify a lung lesion during operation. We report the use of intraoperative intrathoracic video-assisted ultrasonography to localize a lung tumor before its removal.

Case Reports

Patient 1

A 67-year-old man was diagnosed as having a central left upper lobe cancer. Because of severe lung dysfunction due to emphysema, the patient was thought not to be a candidate for pneumonectomy. He received curative radiotherapy to the left lung and mediastinum. This resulted in complete radiological response. On a routine 3-month follow-up 1½ years later, the patient was noted to have a 2-cm peripheral nodule in the apical segment of the right upper lobe. At that time, in addition to severe emphysema, radiation pneumonitis to the left lung had also developed (Fig 1). A transthoracic needle aspiration of the right upper lobe nodule confirmed the lesion to be histologically different, ie, second primary lung cancer. The patient was discussed at a Lung Tumor Board meet-

ing and it was thought that the best therapeutic option available to this patient would be an attempt for video-assisted thoracoscopic wedge resection of the right upper lobe lesion.

On the day of the operation, the patient was taken to the radiology department where a 21-gauge breast localization needle was inserted into the tumor under computed tomographic guidance as previously described [4]. After the procedure, tension pneumothorax developed, which necessitated a tube thoracostomy.

The patient was then taken to the operating room. Under general anesthesia with selective left endobronchial intubation, he was put in the right lateral position and the right lung collapsed. Endobronchial suctioning was used to ascertain complete deflation of the right lung. Three thoracic ports were used: two in the anterior and posterior fourth intercostal space and one in the midaxillary sixth intercostal space. The posterior port was used for the purpose of inserting the ultrasonography probe. We used a transvaginal transducer with a convex probe operating at 5 MHz with a portable ultrasound unit (SSD 500; Aloka Inc) (Fig 2). The wire was found displaced in the pleura. The tumor and its margins were clearly defined by ultrasonography, which allowed appropriate positioning of the linear stapling device before firing. At completion of the resection, the operative specimen was further assessed ex vivo by ultrasonography and compared with preresection images to confirm that the tumor was removed in total.

Patient 2

An 83-year-old woman with a new 1.4-cm peripheral right upper lobe nodule was thought to be too frail to undergo thoracotomy for resection. Preoperative evaluation including computed chest tomography confirmed the lesion to be radiologically T1 N0 M0 (Fig 3). A decision was made to resect the nodule thoracoscopically. The patient underwent needle localization of the peripheral tumor under computed tomographic guidance immediately before operation. Thoracic ports similar to those in patient 1 were used. At the time of the operation, the tip of the wire was found to be displaced in the pleura. Methylene blue dye, which was injected simultaneously with needle localization, facilitated identification of the particular region of the lung to be scanned by ultrasonography. A 10-mm rectal probe with a side transducer operating at 5 MHz and a similar ultrasound unit were used to localize the lesion. Interestingly, the lesion was found to be 2 cm away from the methylene blue stain used simultaneously with the needle localization technique. The lesion was

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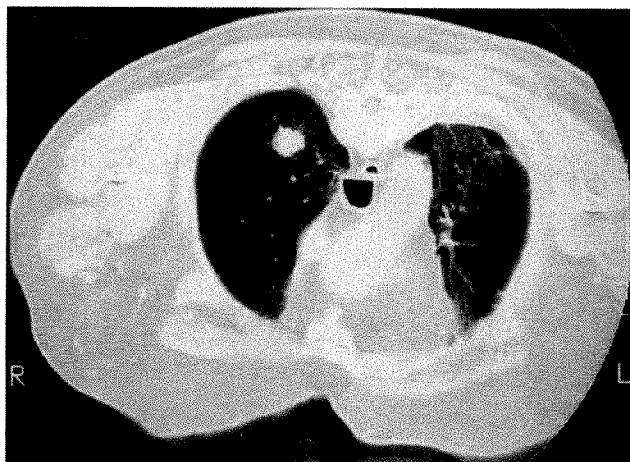


Fig 1. Thoracic computed tomogram of patient 1. Note the effects of radiation pneumonitis bilaterally and the depth of the lesion in the right upper lobe.

resected widely using linear staplers under direct ultrasonography guidance. The patient had an uneventful recovery.

Comment

Video-assisted thoracoscopic resection is increasingly used for diagnostic and therapeutic purposes. In primary lung cancer, it is currently indicated for high-risk patients who could not tolerate a lobectomy. Metastasectomy and excisional biopsy of other lesions through such minimally invasive procedures may also be advantageous. Although not documented objectively, video-assisted thoracic surgery is perceived to cause less postoperative pain and have shorter duration of hospitalization.

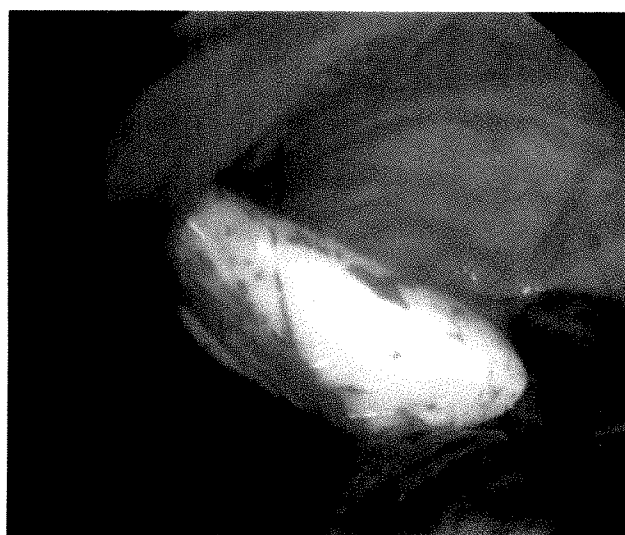


Fig 2. Ultrasound transducer probing the surface of the right upper lobe. A grasper is used to fix the area of the lung being examined. Fluid is injected into the probe-indented area of the lung to improve surface contact of the transducer.

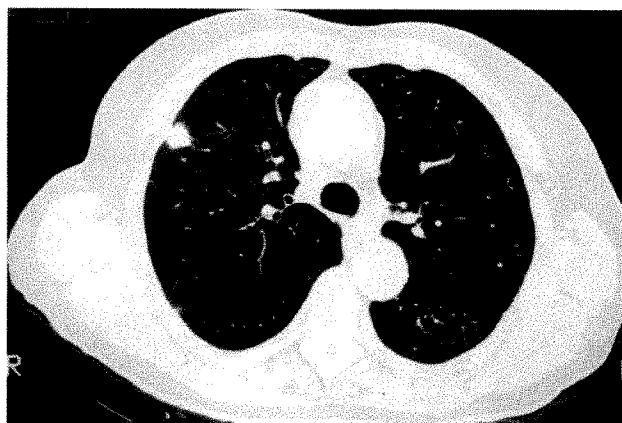


Fig 3. Thoracic computed tomogram of patient 2. Note the 1.4-cm peripheral nodule in the right upper lobe.

An important limitation to video-assisted thoracic surgery is the difficulty in identifying lung lesions as palpation of the lung is not always possible. The use of metal probes intraoperatively does not compensate for the tactile discrimination lost. Even when needle localization is used, it is frequently difficult to define the depth and margins of the lesion to be resected. The use of an ultrasonography probe may provide numerous advantages: (1) It allows identification of the site of the tumor. As the lung is collapsed, the lung lesion may not settle at the same location that it is perceived to be at based on the computed tomographic scan of an inflated lung. (2) Intraoperative intrathoracic ultrasonography may facilitate not only localization of the lesion but also definition of its margins and hence planning of the strategy of resection, eg, stapling or laser. (3) It allows visualization of the relation of the lesion to important vascular and bronchial structures, which may determine the direction of the linear stapling. (4) As linear staplers are applied, the ultrasound probe may be used to guide the placement of these linear staplers and the progression of cutting to safely encompass the whole lesion. (5) At completion of resection it is possible, by repeating the ultrasonographic assessment of the specimen *ex vivo* and by comparing it with preresection images, to ascertain that the lesion has been removed in total.

Although ultrasonography of the lung is not feasible in its inflated state, once the lung is collapsed, it becomes easily scanned. The residual air in the bronchial tree is visible as branching reverberating artifacts, small and larger vessels are also seen, and solid tumors become distinct from the remainder of lung parenchyma. In these 2 cases, we used a 25-mm transvaginal transducer or a 10-mm rectal transducer with a relatively long shaft, which allows manipulation from outside the thorax. By angulating the probe over the collapsed lung, it is possible to scan the whole surface of the lung. A frequency of 5 MHz was sufficient to scan deep enough into the lung parenchyma with adequate quality of imaging in the near field. Filling the pleural cavity with saline solution or indenting the surface of the pleura by gentle pressure

from the tip of the probe together with injection of saline solution locally will improve surface contact of the transducer and result in better resolution. Use of probes with end rather than side transducers, in our opinion, allows for easier maneuvering and scanning of the lung through the restricting thoracic ports. It is likely that other transducers will be developed and used in the future, hopefully with a smaller diameter and a longer shaft. Intraoperative ultrasonography is likely to become the method of choice for localization of occult lesions either alone or together with the technique of needle localization. The latter has numerous disadvantages such as wire dislodgement, logistical difficulties due to timing of the imaging procedure and scheduling of the operation, and the risk of pneumothorax. Marking of the pleural surface of the lung with methylene blue dye, on the other hand, can be very helpful as it can define and restrict the region to be scanned by operative ultrasonography. Our current preference for localization of occult lung lesions is to take the patient to the radiology suite immediately before the operation. The lesion is localized by methylene blue and a

wire under computed tomographic guidance. Intraoperative ultrasonography is then used at the time of thoracoscopy to confirm the site and relation of the tumor and to guide the application of staplers or laser resection.

In summary, this report describes the applicability of intraoperative intrathoracic ultrasonography to localize lung tumors and resect them by video-assisted thoracic surgery.

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Management of Patent Saphenous Vein Grafts During Reoperative Coronary Artery Bypass Grafting

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A patient was referred for coronary artery bypass reoperation. After a left internal mammary artery was grafted to the left anterior descending coronary artery, the diseased but patent old saphenous vein graft was ligated. This resulted in severe myocardial failure, which was

corrected only after restoration of flow through the old vein graft. We suggest the decision to ligate or replace an old vein graft should be individualized to avoid the risk of myocardial ischemia.

(Ann Thorac Surg 1993;55:770-1)

Controversy still persists as to the management of partially stenosed or patent vein grafts in patients undergoing reoperative coronary artery bypass grafting. The risk of myocardial ischemia or infarction due to intraoperative embolization of atherosclerotic debris from within existing vein grafts was clearly demonstrated by Keon and colleagues [1]. This has prompted some authors to recommend early proximal ligation of existing vein grafts and replacement of patent vein grafts 5 years old or older at the time of reoperation [2, 3]. We report a case that illustrates the problems associated with ligating a diseased but patent vein graft to the left anterior descending (LAD) coronary artery and replacing it with an internal mammary artery (IMA) graft.

A 61-year-old man was referred for reoperative coronary artery bypass grafting. In 1980 he had undergone coronary bypass with saphenous vein grafts to the LAD coronary artery, right coronary artery, and marginal branch of the circumflex artery. In September 1991 he was hospitalized with unstable angina. Coronary angiography revealed a patent saphenous vein graft to the LAD coronary artery with diffuse luminal irregularities causing up to 40% narrowing. The vein grafts to the circumflex and right coronary arteries were completely occluded, as were all his native arteries. Overall left ventricular function was well preserved.

At reoperation the left IMA (LIMA) was dissected as a pedicle while the remaining long saphenous vein was harvested. The LIMA measured more than 2 mm in diameter with a brisk flow. Intrapericardial adhesions were carefully divided, taking care not to disturb the patent vein graft. After establishment of cardiopulmonary bypass, standard intermittent cold-blood cardioplegic arrest was used to perform three distal anastomoses using

the LIMA to the LAD coronary artery, distal to the old vein graft, and two segments of reversed saphenous vein to the distal right and obtuse marginal coronary arteries. Adequate flow down the LIMA was assured by observing, upon release of the bulldog clamp on the LIMA, the immediate filling of the distal LAD coronary artery and its branches, the rapid return of left ventricular mechanical activity, and the sharp rise in left ventricular apical temperature measured routinely by a myocardial probe. The flows through the vein grafts were measured by the perfusionist during infusion of cardioplegic solution down them (120 mL and 90 mL, respectively, at 100 mm Hg pressure). After the aortic cross-clamp was removed, the heart spontaneously went into a slow sinus rhythm. At this time the old graft to the LAD coronary artery was ligated, after which the heart promptly fibrillated and had to be defibrillated twice. A partial occlusion clamp was applied to the ascending aorta, and the proximal anastomoses of the right coronary and obtuse marginal vein grafts were performed.

Heart contractility and the electrocardiogram appeared normal on cardiopulmonary bypass. Several attempts were made to wean the patient off cardiopulmonary bypass. However, there was evidence of severe left ventricular failure with ischemic anterior wall electrocardiographic changes. An intraaortic balloon pump was inserted through the left common femoral artery. Despite intraaortic balloon pump support hemodynamic instability persisted. At this time it was surmised that the anterior wall of the left ventricle was not receiving sufficient blood from the LIMA graft.

The ligature on the old vein graft was removed and the graft opened proximally to ensure adequate retrograde flow from the LIMA and to wash out atheromatous debris once flow was restored through this graft. The patient was promptly weaned off cardiopulmonary bypass without difficulty and remained hemodynamically stable without pharmacologic or intraaortic balloon pump support. The patient made an uneventful postoperative recovery.

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Comment

Grondin and associates [3] have shown that early vein graft manipulation during reoperative coronary artery bypass grafting can result in embolization of atheroma from within vein grafts by mechanical disruption. They recommend early proximal ligation of vein grafts after minimal dissection to initiate cardiopulmonary bypass. In a recent study by Campos and colleagues [4] there was no difference in progression of atherosclerosis between vein grafts that were normal at 5 years and those that had minimal disease. These results suggest that the risk of occlusion or stenosis in vein grafts that have minimal stenoses at 5 years postoperatively is comparable with that in new vein grafts. We agree with minimizing manipulation of vein grafts during reoperation, but believe the decision to ligate or replace an old vein graft should be individualized.

Superior long-term patency rates of IMA grafts have been clearly demonstrated [5]. Concerns have persisted, however, about their possible flow limitations. According to the Poiseuille equation, IMA flow is limited by its internal radius and to a much lesser extent by its length. Flemma and colleagues [6] showed that resting flows through vein grafts were 2.7 times those through IMA grafts. In addition, they presented evidence that the saphenous vein has a greater capacity to increase its flow during periods of increased demand. Intraoperative papaverine is commonly used to increase the size of the IMA and facilitate its use [7]; however, if a large segment of the anterior wall is to be acutely dependent on IMA flow, there will still be instances of perioperative myocardial failure, as occurred in our case, and perhaps longer term myocardial ischemia [8]. To avoid the potential for inadequate flow to a large subserved myocardial mass during

early reperfusion, we recommend leaving a patent saphenous vein graft unligated, thus maintaining dual supply to the coronary vasculature. The IMA graft should remain patent even when competing with a high-flow vein graft as it has been shown to maintain its patency under no-flow situations [9].

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Thoracoscopic Transdiaphragmatic Approach for Adrenal Biopsy

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The role of thoracoscopy for the management of intrathoracic diseases has expanded with advancement in endoscopic instrumentation and technology. We report a case of thoracoscopic transdiaphragmatic biopsy of an adrenal gland for metastatic carcinoma. The procedure was uncomplicated and the patient was discharged on the sec-

ond postoperative day. The morbidity of traditional approaches for adrenal operation was avoided. Thoracoscopy may be a useful approach in selected patients for adrenal operation.

(*Ann Thorac Surg* 1993;55:772-3)

Numerous surgical approaches to the adrenal gland have been described including anterior, posterior, flank, and thoracoabdominal techniques [1]. Advances in endoscopic surgical instrumentation have expanded the role of thoracoscopy in the management of many intrathoracic conditions. This report describes the successful thoracoscopic transdiaphragmatic biopsy of an adrenal gland.

A 58-year-old man presented with a new left adrenal mass. The patient had a history of a right colectomy for adenocarcinoma 6 years previously. He had a recurrence in his liver, which was successfully treated with intrahepatic 5-fluorouracil. Six months before presentation, he had resection of three metastases in his right lung by thoracoscopic laser techniques. By computed tomography performed in follow-up after this procedure, a new 3.0-cm mass in his left adrenal gland was discovered (Fig 1). A percutaneous needle biopsy of the mass yielded normal adrenal tissue.

To gain tissue confirmation of metastatic disease an open biopsy was thought to be indicated. After induction of anesthesia, a double-lumen endotracheal tube was used to collapse the left lung. A 10-mm telescope and camera (OTV-52; Olympus Corp, Lake Success, NY) was introduced into the chest through a trocar (Surgiport; United States Surgical Corp, Norwalk, CT) placed posterior to the midaxillary line in the ninth intercostal space. No intrathoracic abnormalities were observed. Two additional trocars were placed anteriorly and posteriorly in the ninth and tenth intercostal spaces as access for endoscopic scissors and grasping instruments. A 6-cm radial incision was made posteriorly in the diaphragm to access the retroperitoneum. Using careful sharp and blunt dissection, exploration of the retroperitoneal fat was undertaken until Gerota's fascia was identified. The fascia was opened

superiorly, and an enlarged adrenal gland was identified. An endoscopic fan retractor was used to facilitate exposure. The blood supply to the adrenal gland was managed with endoscopic surgical clips. A biopsy forceps was used to obtain tissue for microscopic analysis, which confirmed metastatic adenocarcinoma in the adrenal gland. The procedure was terminated at that point, but if indicated, complete resection of the adrenal gland could have been easily accomplished. The diaphragm was then reapproximated using the endoscopic hernia stapler (Endo Hernia Stapler; United States Surgical Corp). A chest tube was not used, and the trocar sites were closed with an absorbable subcuticular suture. Total operating time was 135 minutes.

The patient's postoperative course was unremarkable. He was discharged on the morning of the second postoperative day. No parenteral pain medication was required to manage the mild incisional discomfort. The patient resumed full activity on the fourth postoperative day and is presently undergoing chemotherapy. A chest roentgenogram remains normal 4 months postoperatively with no evidence of diaphragmatic herniation.

Comment

Thoracoscopy has had a limited application, until recently, for management of intrathoracic diseases. Improvement in optics, video technology, endoscopic lighting sources, and endoscopic instrumentation have expanded the role of thoracoscopy to include procedures involving the lung, pericardium and mediastinum, and pleura [2].

There are multiple indications for surgical intervention on the adrenal gland. The approach is partially dictated by the adrenal pathology. The anterior transabdominal approach is indicated for lesions that are either large or potentially malignant. It is also indicated for pheochromocytoma to allow for early vascular control and to allow for exploration for bilateral or extraadrenal tumors [3].

The posterior surgical approach was described by

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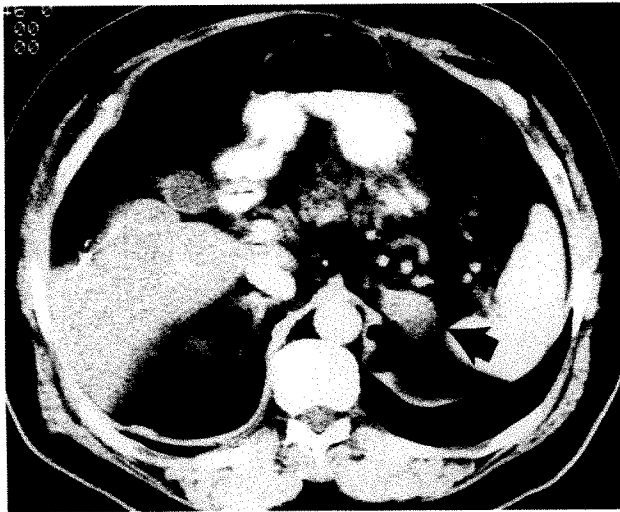


Fig 1. Computed tomogram demonstrating a left adrenal mass (arrow).

Young [4] more than 50 years ago and is anatomically the most direct route to the adrenal gland. Although the morbidity of this approach is less than with the anterior route, the operative field is relatively small and exposure is restricted. A flank incision has been advocated as being helpful for adrenalectomy in obese patients [3]. The thoracoabdominal approach is usually reserved for large right-sided adrenal masses.

The morbidity associated with adrenalectomy can be as high as 40%, and the mortality is approximately 2% to 4% depending on the indication and approach [5, 6]. The morbidity and pain associated with traditional surgical incisions serve as an impetus to minimally invasive surgical techniques. Thoracoscopy offers the advantage of lessened morbidity from the surgical incision, yet excellent exposure of the retroperitoneum due to optics, magnification, and lighting.

The thoracoscopic approach would not be indicated in patients with pheochromocytoma or large adrenal masses for resection. There are, however, a select group of patients in whom this may become the preferred technique. In our case, we performed a limited biopsy on the

adrenal gland only after a percutaneous needle biopsy was nondiagnostic.

Enlarged adrenal glands are encountered in otherwise operable patients (4.1%) with non-small cell lung cancer [7]. Frequently, there is discovered pathology other than metastatic carcinoma including adenomas, hyperplastic nodules, and cysts. Preoperative percutaneous needle biopsy should first be performed. If nondiagnostic, thoracoscopy at the time of anticipated lung resection could then be used to obtain a definite tissue diagnosis if both lesions were on the same side.

Reyes and associates [8] have reported prolonged survival of 5 patients with lung cancer and adrenal metastases in whom the primary tumor was resected and adrenalectomy performed. Both resections could be managed by thoracoscopy.

In summary, thoracoscopy offers a new approach for operation on the adrenal gland. More experience is necessary before the scope of procedures possible can be determined. In selected patients, the thoracoscopic transdiaphragmatic approach offers lessened morbidity and superior visualization compared with open approaches. As minimally invasive surgical techniques improve, continued modification of standard surgical approaches is likely to happen.

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Infected Hepatic *Echinococcus* Cyst Presenting as Recurrent *Escherichia coli* Empyema

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An 81-year-old man, previously a shepherd in Italy, presented with recurrent *Escherichia coli* empyema over an 8-month period. His empyema was caused by an infected, nonviable hepatic *Echinococcus* cyst that eroded the diaphragm and led to intermittent spillage and pleural seeding. This case demonstrates that when dealing

with *Escherichia coli* empyema, a subdiaphragmatic source ought to be suspected, and among immigrants from areas with prevalent hydatid disease, infected hepatic *Echinococcus* cyst might rarely be the cause.

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Escherichia coli is a rare cause of empyema usually associated with *Escherichia coli* pneumonia and less frequently, with spontaneous bacterial peritonitis [1, 2]. Additionally, an intraabdominal focus, such as subphrenic abscess, may erode through the diaphragm and lead to the development of empyema [3]. In all of these circumstances, recurrence of empyema is extremely rare. Recurrence is usually due to inadequate therapy or may represent new seeding of the pleural space because of unrecognized fistula. We present a case of recurrent *Escherichia coli* empyema over an 8-month period due to infected, nonviable hepatic *Echinococcus* cyst.

An 81-year-old man, who was previously a shepherd in Italy, experienced sudden onset of fever, right-sided pleuritic chest pain, and dyspnea. His symptoms included vague abdominal pain, decreased appetite, and a 13.5-kg weight loss over the last 8 months. His medical history was remarkable for hospitalization for right-sided *Escherichia coli* empyema 30 days earlier. He was treated with chest tube drainage and a 14-day course of cefazolin, which was completed 17 days before his admission. He was also hospitalized elsewhere several months earlier with "pneumonia and pleurisy," which was verified later to be *Escherichia coli* empyema without pneumonic process.

His physical examination demonstrated a temperature of 38°C, dullness, absent breath sounds, and decreased vocal fremitus over the right hemithorax plus moderate right upper quadrant abdominal tenderness. His laboratory tests demonstrated the presence of leukocytosis ($11.3 \times 10^9/L$; 78% polymorphonuclear leukocytes), normal serum bilirubin level (6.8 $\mu\text{mol/L}$ [0.4 mg/dL]), and elevated levels of alkaline phosphatase (360 IU/L; normal range, 15 to 130 IU/L), alanine aminotransferase (58 IU/L; normal range, 0 to 45 IU/L), and aspartate aminotrans-

ferase (48 IU/L; normal range, 0 to 40 IU/L). His chest roentgenogram demonstrated the presence of right pleural effusion. Repeat thoracentesis showed grossly purulent fluid that grew *Escherichia coli*. At this point, a subphrenic source of his recurrent empyema was suspected.

Computed tomography of the abdomen was performed. It showed a large calcified cyst (Fig 1). Upon questioning, the patient stated that he was aware of this cyst for many years. It was thought to be an inactive *Echinococcus* cyst based on its characteristic calcification and its stable size over many years of follow-up. For this reason, needle aspiration or closed drainage procedures were not attempted because of fear of anaphylaxis and to avoid spreading potentially quiescent parasite. He underwent exploratory laparotomy, and the cyst was resected. It was found to be communicating through the diaphragm with the right hemithorax and to contain purulent material, which subsequently grew *Escherichia coli*. Microscopic examination of the cyst failed to show any scolex or viable germinal layer. He was treated with intravenous ceftriaxone (1 g/day) and gentamicin (2.5 mg/kg every 18 hours) for 14 days followed by 14 more days of oral ciprofloxacin (500 mg twice per day). He improved remarkably after operation and became asymptomatic with no further recurrences of his empyema.

Comment

Empyema is a recognized complication of pneumonia, bronchopleural fistula, esophageal perforation, or, rarely, a subphrenic source eroding the diaphragm [3, 4]. Although its cause is usually apparent at the time of diagnosis, occasionally the presenting manifestations may not be specific enough for precise determination. In these circumstances, the bacterial cause may help in identifying its source. For example, isolating common respiratory pathogens such as *Streptococcus pneumoniae* or *Haemophilus influenzae* usually indicates a community-acquired pneumonia as the primary pathologic condition. In another

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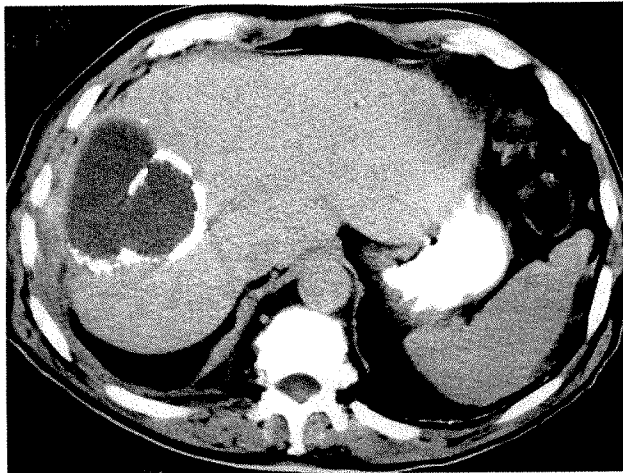


Fig 1. Computed tomogram of the abdomen showing a large, calcified hepatic *Echinococcus* cyst.

instance, the presence of mouth anaerobes may lead to the diagnosis of aspiration pneumonia, ruptured lung abscess, or esophageal perforation. Likewise, isolation of enteric pathogens such as *Escherichia coli*, especially in the absence of pneumonia, should point to an abdominal source with hematogenous spread to the pleura or direct extension through the diaphragm. In our patient, the cause was found to be an infected "burned out" hepatic *Echinococcus* cyst.

We believe that this patient acquired echinococcosis as a shepherd in Italy. His cyst then became nonviable and

calcified. Subsequently, it got secondarily infected, probably from a biliary source. Then infection spread to the dome of the liver and the diaphragm, creating a fistula into the right hemithorax leading to intermittent leakage to the pleural space and recurrent empyema.

Because *Echinococcus* is most prevalent in the Middle East, Australia, New Zealand, eastern and central Europe, and Latin America [5], it should be considered in immigrants of these areas who present with empyema caused by enteric pathogens, particularly in the presence of a cystic defect in the liver. Then proper surgical drainage can be carefully done to avoid scolex spillage and spread of infection [6, 7].

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Successful Combined Operation for Mitral Stenosis and Atrial Fibrillation

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Simultaneous surgical treatment of mitral stenosis and atrial fibrillation was performed. The patient's postoperative course was uneventful, the rhythm changed to sinus rhythm, and the patient was discharged on the 21st postoperative day in stable condition.

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Most patients with mitral valve disease have suffered from atrial fibrillation (AF) that produces poor hemodynamic conditions and increases the chance of a thromboembolic event. Recently, Cox and his colleagues [1, 2] described the operative technique for the surgical treatment of AF in patients without valvular disease. Atrial fibrillation combined with valvular heart disease often causes difficult postoperative management and decreases the quality of life. These concerns make it very important for those patients suffering from both diseases to undergo simultaneous surgical treatment for the valvular heart disease and AF.

A 54-year-old man was admitted with exertional dyspnea and tachycardic arrhythmia. Echocardiography and cardiac catheterization revealed severe mitral stenosis with mild pulmonary hypertension and thrombus issuing from the appendage in the enlarged left atrium.

The heart was exposed by a median sternotomy. To complete the bypass and to use moderate hypothermia, the aorta was cross-clamped, and modified Young's solu-

This incision was carried caudally to the inferior limbus, and cranially the incision was continued through the roof of the left atrium to the left atrial appendage.

The exposure of the entire mitral annulus was facilitated by placing several retraction sutures; calcified valve and large organized thrombus were recognized and resected carefully. In modifying the maze procedure reported by Cox, we performed a left atrial incision as follows. A vertical posterior left atriotomy was placed 5 mm from the center of the posterior mitral valve annulus to the midway point between the left and right inferior pulmonary veins to expose the fat pad at the atrioventricular groove. In placing this incision, we took care to avoid injuring the circumflex coronary artery, esophagus, and coronary sinus. The incision was extended superiorly to carry between the left and right superior pulmonary veins until it joined the previously placed superior transverse left atriotomy. The posterior left atriotomy was then closed with a continuous 3-0 monofilament suture. After this procedure, we performed mitral valve replacement using a 25-mm Björk-Shiley valve. The transverse atriotomy on the top of the left atrium was then extended into the base of the left atrial appendage, and the appendage was excised. The transverse left atriotomy was closed, beginning at the lateral base of the excised left atrial appendage (Fig 1B). The atrial septotomy was also closed from the bottom of the fossa ovalis toward the top of the atrial septum. The two suture line closures were then secured, which closed the left side of the heart.

Finally we performed the right atrial incisions (Fig 1C). The right atrial incision was made from the superior base of the excised right atrial appendage into the anterior superior vena cava. Then a counterincision was placed in the posterior right atrial free wall, beginning well up into the superior vena cava posteriorly. The posterior right atriotomy was then carried down the lateral free wall of the right atrium and was curved anterior to the inferior vena cava cannula. This incision was carried to the level of the tricuspid valve annulus just posterior to the orifice of the coronary sinus carefully to avoid injury to the right coronary artery. After these incisions were completed, the aortic cross-clamp was released and the left side of the heart was deaired. The right atrial incisions were closed from the posterior wall to the lateral wall with a continuous 4-0 monofilament suture. The aortic cross-clamp time was 123 minutes.

After defibrillation, the heart began beating with junc-

For editorial comment, see page 578.

tion and glucose-insulin-potassium cardioplegic solution were given to arrest and protect the heart. We chose the superior-transseptal approach to the left atrium [3], considering it to be mutually beneficial to the mitral valve procedure and to atrial incisions (Fig 1A).

The right atrium was opened obliquely laterally from the inferior venous cannula to the medial part of the right atrium where it meets the roof of the left atrium. Care was taken not to damage the sinus node. The interatrial septum was opened longitudinally at the fossa ovalis.

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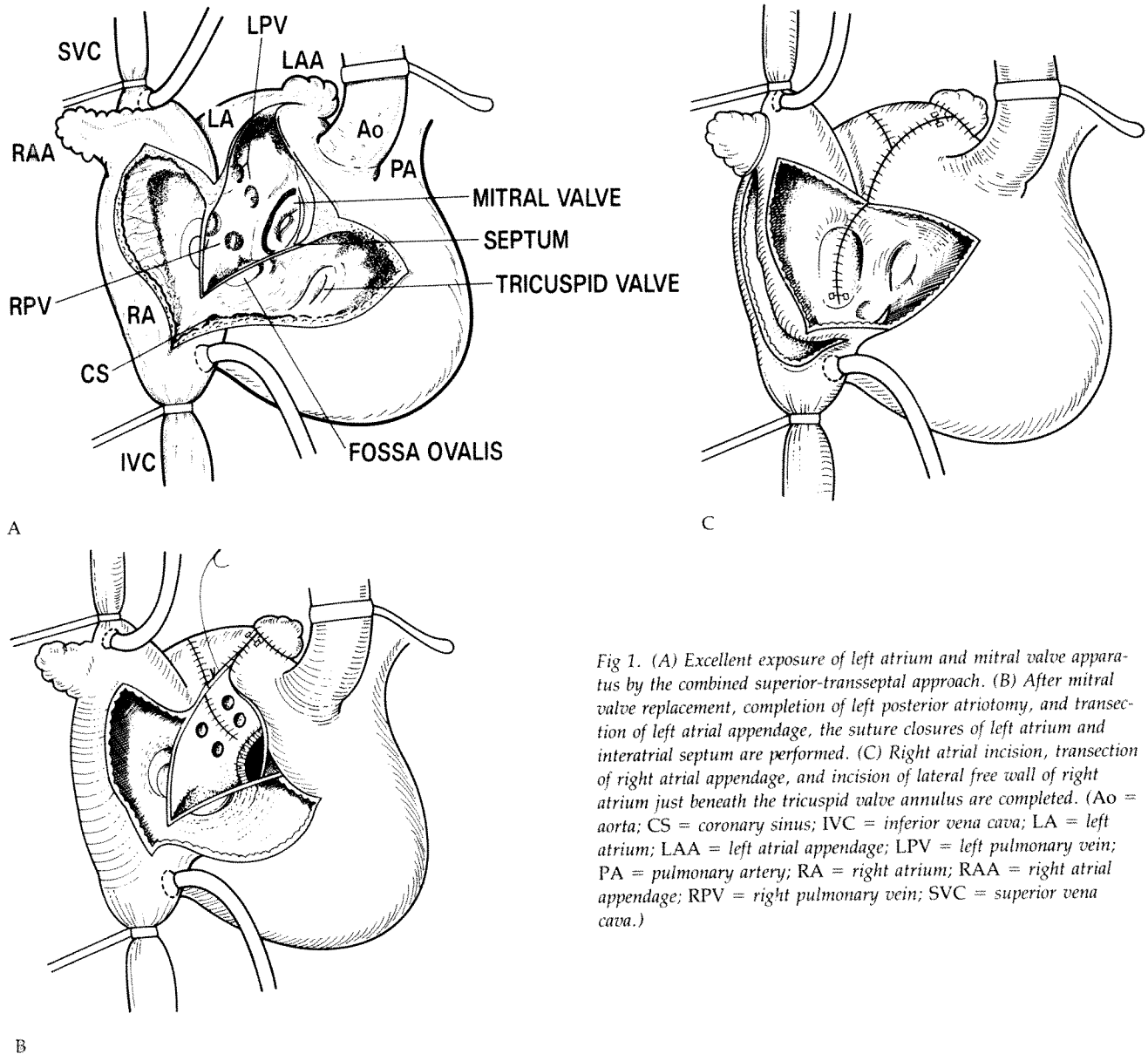


Fig 1. (A) Excellent exposure of left atrium and mitral valve apparatus by the combined superior-transseptal approach. (B) After mitral valve replacement, completion of left posterior atriotomy, and transection of left atrial appendage, the suture closures of left atrium and interatrial septum are performed. (C) Right atrial incision, transection of right atrial appendage, and incision of lateral free wall of right atrium just beneath the tricuspid valve annulus are completed. (Ao = aorta; CS = coronary sinus; IVC = inferior vena cava; LA = left atrium; LAA = left atrial appendage; LPV = left pulmonary vein; PA = pulmonary artery; RA = right atrium; RAA = right atrial appendage; RPV = right pulmonary vein; SVC = superior vena cava.)

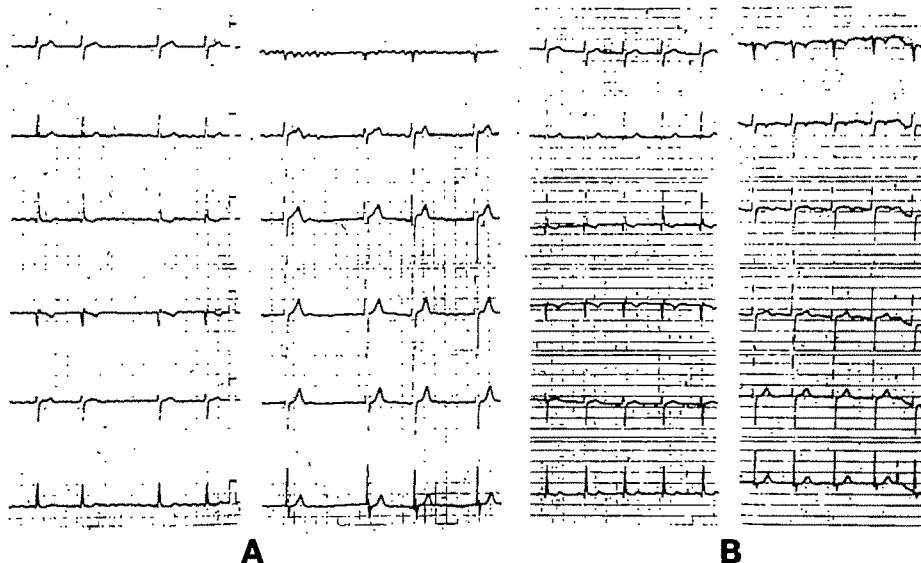
tional rhythm and the patient was decannulated after the intraaortic balloon pump catheter was inserted. The patient was weaned from the ventilator and intraaortic balloon pump the following day. His postoperative course was uneventful and his heart rhythm showed mainly junctional rhythm for the first week postoperatively (Fig 2). Subsequently, his heart rhythm was converted to sinus rhythm. Cardiac catheterization 3 weeks after the operation confirmed satisfactory postoperative status. He remains well, active, and at work 6 months postoperatively with no evidence of AF.

Comment

Atrial fibrillation develops in 40% to 50% of patients with mitral stenosis [4]. It impairs cardiac performance and

predisposes the patient to systemic emboli. In particular, after valve replacement tachycardic AF resistant to medical treatment decreases cardiac output, and because of the arising severe low output syndrome the postoperative course often becomes eventful. The concept and operative method of surgical treatment of AF was first described in 1991 by Cox and his colleagues. They performed this operation on 14 patients without valvular disease and were rewarded with a successful outcome in all cases. Because we were convinced that this operation would benefit the patient suffering from mitral valvular disease and AF, we performed a simultaneous operation to treat both mitral stenosis and AF. The successful outcome of our case supports our confidence that the simultaneous mitral valve and AF operation will witness widespread clinical application.

Fig 2. Preoperative (A) and postoperative (B) electrocardiogram.



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Technique of Transplantation for Hypoplastic Left Heart Syndrome With Left Superior Vena Cava

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The presence of a left superior vena cava in infants with hypoplastic left heart syndrome complicates the technical performance of orthotopic cardiac transplantation. In this report we describe a modification of the recipient cardiectomy to maintain patency of the left superior vena cava, leaving the recipient coronary sinus as a conduit for it into the right atrium and avoiding complex venous reconstructions.

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Orthotopic cardiac transplantation for hypoplastic left heart syndrome has become increasingly common after the initial reports by Bailey and associates [1]. The technique of infant cardiac transplantation has been previously described [2]. The presence of an anomalous left superior vena cava (LSVC) entering the coronary sinus of the recipient infant with hypoplastic left heart syndrome, however, presents a problem for orthotopic cardiac transplantation. Previous descriptions of methods of dealing with the LSVC drainage have been oriented toward ligating the LSVC, dividing it and creating an anastomosis to the right superior vena cava, using the donor innominate vein to reconstruct the normal venous drainage, or creating an atrial tunnel [3-5]. Each of these techniques has potential problems. Ligation subjects the patient to risks of unilateral cerebral, facial, and arm edema. Anastomoses of thin-walled veins in neonates are difficult to create without kinking or twisting of the veins. Creating an atrial baffle using pericardium or prosthetic material creates the potential risk of stenosis as the pericardium thickens or an intimal peel forms on the prosthetic material. We have devised an alternative method that leaves the LSVC draining into the coronary sinus *in situ* to avoid the above-mentioned problems and to allow for maximal growth.

Material and Methods

From January 1988 through May 1992, 18 consecutive infants have undergone orthotopic cardiac transplantation for hypoplastic left heart syndrome at St. Louis Children's Hospital, Washington University Medical Center. Three of these infants underwent transplantation after a first-stage Norwood operation for hypoplastic left

heart syndrome. Four of the 18 infants referred for transplantation had an associated large LSVC entering the coronary sinus. The recipient cardiectomy was altered slightly to permit drainage of the LSVC through the coronary sinus orifice into the recipient right atrium to maintain LSVC flow after transplantation.

After hypothermic circulatory arrest, the cannulas for cardiopulmonary bypass are removed from the heart. An incision is made in the anterior wall of the right atrium of the recipient and carried inferiorly below the orifice of the coronary sinus and outside of the heart (Fig 1). The incision is carried superiorly across the roof of the left atrium, leaving as much of a rim of tissue as possible; occasionally the left atrial appendage is left in place to allow sufficient tissue for reconstruction of the left atrium because the LSVC courses posteriorly behind the left atrium entering the coronary sinus in the left atrioventricular groove. When the left atrial appendage is left in place it may be opened longitudinally to its apex to provide more atrial tissue for the anastomosis and also to prevent it from becoming a site for thrombus formation. The atrial septum is divided superior to the coronary sinus orifice. Excision of the heart is completed by incising the left atrioventricular groove above the coronary sinus, dividing the posterior descending and great cardiac veins in the process. Occlusion of the veins can be performed either by individual ligation or by incorporating the veins in the left atrial suture line while implanting the donor heart. The aorta is reconstructed as usual for hypoplastic left heart syndrome. The recipient coronary sinus becomes in effect a conduit for the LSVC with its orifice in the right atrium. In our patients absorbable suture was used for all anastomoses to allow for maximum growth.

Results

All 18 infants are hospital survivors. There has been one late death secondary to chronic pulmonary venous obstructive disease 2 months after transplantation in an infant who had initially been treated with a first-stage Norwood procedure at 1 day of life. Another infant has undergone retransplantation at 1 year of age after acquiring severe transplant coronary artery disease when administration of steroids was discontinued. All 4 infants who had the described repair of the LSVC drainage have done well with no clinical evidence of venous hypertension in the left upper body. Echocardiograms have shown patency of the LSVC with excellent flow into the right atrium in each patient (Fig 2). In 2 infants, a Broviac

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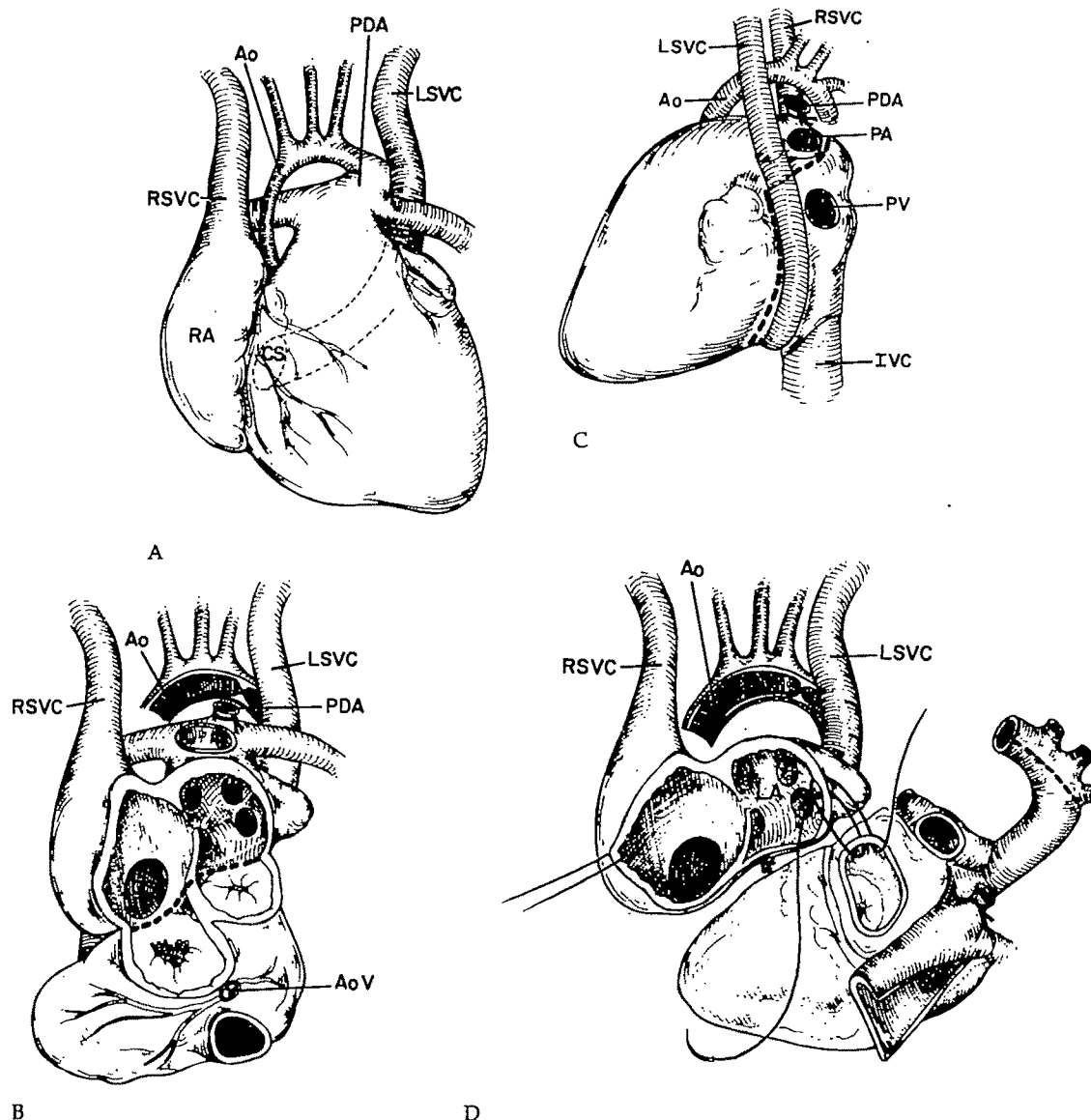
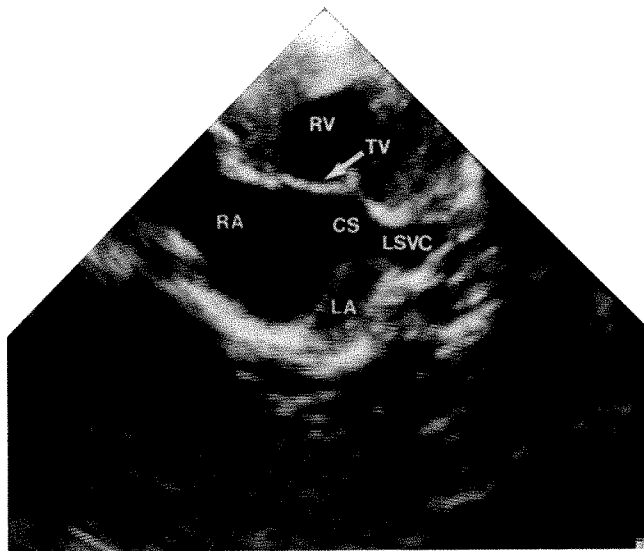


Fig 1. (A) Anatomy typical for hypoplastic left heart syndrome with left superior vena cava (LSVC) draining into the right atrium (RA) through the coronary sinus (CS), which is enlarged. (B) The recipient cardiectomy incision in the right atrium is carried outside the heart inferior to the orifice of the coronary sinus near the atrioventricular groove. (C) This is a left anterior oblique view of the heart showing the recipient cardiectomy incision (dotted line) coursing along the roof of the left atrium behind and lateral to the pulmonary artery (PA), then anterior to the LSVc, and finally near the left atrioventricular groove. (D) Anastomosis of the donor and recipient left atria includes the great cardiac and posterior descending coronary veins in the suture line; anastomosis of donor and recipient right atria leaves the recipient CS entering the RA and thus maintains LSVc patency. (Ao = aorta; AoV = aortic valve; IVC = inferior vena cava; PDA = patent ductus arteriosus; PV = pulmonary vein; RSVC = right superior vena cava.)

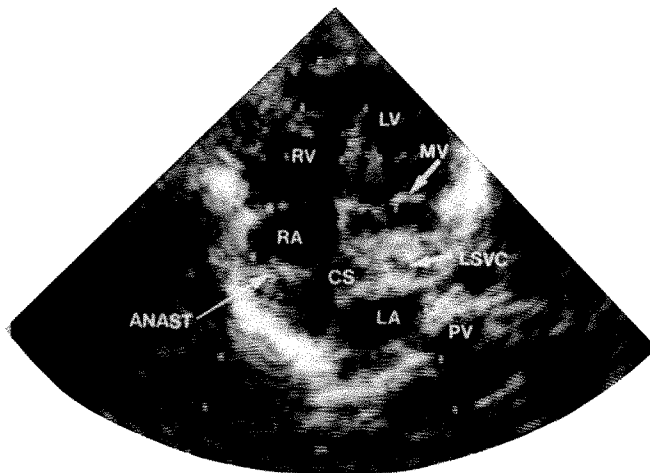
catheter (Bard Access, Salt Lake City, UT) was placed in the LSVc for blood drawing and intravenous antibiotic therapy (Fig 3), with maintenance of the right superior vena cava for use for endomyocardial biopsy for postoperative monitoring of immunosuppression. The time required for cardiac transplantation was longer for those infants with LSVc; total pump (including circulatory arrest time) and circulatory arrest times for those with LSVc were 113.5 ± 15.6 and 50.5 ± 7.6 minutes, respectively, versus 105.8 ± 4.8 and 41.2 ± 7.2 minutes for those with normal great veins.

Comment

Although many approaches have been described for complex congenital reconstructions with orthotopic cardiac transplantation, a common associated condition in hypoplastic left heart syndrome appears to be the persistence of the LSVc draining into the coronary sinus (22% in our series). As described above, minor alterations in the recipient cardiectomy can facilitate dealing with the LSVc and obviate complex venous reconstructions in infants with hypoplastic left heart syndrome, permitting maximal



A



B

Fig 2. (A) Preoperative echocardiogram (modified apical four-chamber view) shows the left superior vena cava (LSVC) entering the coronary sinus (CS) and then into the right atrium (RA). (B) This echocardiogram (apical four-chamber view) performed postoperatively shows the large CS entering the RA just above the level of anastomosis of the donor and recipient right atria. (ANAST = right atrial anastomotic suture line; LA = left atrium; LV = left ventricle; MV = mitral valve; PV = pulmonary vein; RV = right ventricle; TV = tricuspid valve.)

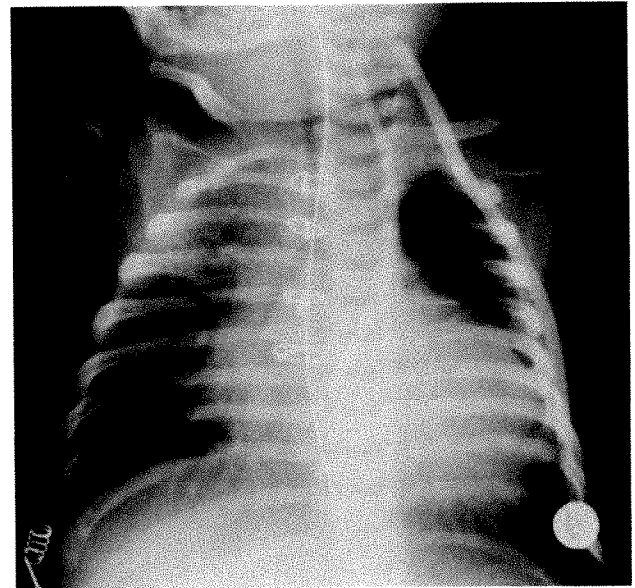


Fig 3. Postoperative chest roentgenogram in an infant after cardiac transplantation showing a Broviac catheter entering the left superior vena cava and the coronary sinus.

opportunity for growth. In rare cases in which the coronary sinus is unroofed into the left atrium, the roof of the coronary sinus can be closed directly before implantation of the donor heart. The technique used in this series can also be used for the adult patient who has an anomalous LSV and requires cardiac transplantation, and is also suitable for use in heart-lung transplantation.

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Localized Supravalvar Aortic Stenosis: A New Technique for Repair

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The deformity in supravalvar aortic stenosis includes generalized thickening of the tissues of the aortic root with a fairly normal sized aortic valve ring. The thickened tissues may obstruct the origins of the left and right coronary arteries. We have repaired 2 cases with complete excision of the stenosing ring below the level of the commissures of the aortic valve into the sinuses, to the level of the left and right coronary arteries.

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Localized supravalvar aortic stenosis is a complex anomaly. As Doty [1] has pointed out, not only is supravalvar stenosing ring present, but also a generalized thickening of the tissues in the region of the ring, the proximal ascending aorta, and the sinuses of Valsalva. The aortic valve is deformed by abnormal commissural proximity, leaving the aortic leaflets redundant and often buckled at the free edge. The ring inhibits full opening of the leaflets and causes a jet lesion of the aortic leaflets, leading to progressive regurgitation. The ring may also impinge on the coronary ostia producing stenosis.

Each sinus of Valsalva resembles a diverticulum with a coronary artery emerging from its cupola, below the stenosing ring. The aortic annulus at the level of the base of the leaflets is usually normal sized.

Case Reports

Patient 1

A 6-month-old boy had a murmur noted in infancy. Echocardiography and cardiac catheterization revealed localized supravalvar aortic stenosis, normal pulmonary arteries, severe left ventricular hypertrophy, and a left ventricle to aorta pressure gradient of 120 mm Hg.

Operation was performed using cardiopulmonary bypass and moderate hypothermia. The thymus was excised. The ascending aorta and the aortic arch and its branches were mobilized from the main pulmonary artery and right pulmonary artery and mediastinal tissues (Fig 1). High ascending aortic and right atrial cannulations were used for bypass, and cardioplegia was administered. The aorta was transected at the level of the stenosing ring, and the thickened tissues were excised from the tops of

the commissures down into the sinuses of Valsalva to the ostia of the left main coronary and right coronary arteries. This freed the commissures to move centrifugally, opening up the region. The distal ascending aorta was transected at a level where it was of normal diameter and free of intimal thickening, 1.5 cm distal to the commissures (Fig 2).

The ascending aorta was anastomosed to the aortic root using continuous 7-0 polypropylene, the suture line running from the apex of the commissures down into each sinus of Valsalva, across the cephalad lip of the left main and right main coronary arteries (Fig 3). The aortic clamp time was 21 minutes. Postoperatively, labile hypertension occurred. Repeat cardiac catheterization 13 months postoperatively revealed no supravalvar gradient (Fig 4), trivial aortic regurgitation, and some regression of the left ventricular hypertrophy.

Patient 2

A 2½-year-old boy with William's syndrome and a heart murmur was found to have supravalvar aortic stenosis. Cardiac catheterization revealed a gradient of 100 mm Hg from left ventricle to aorta with no aortic regurgitation, localized supravalvar stenosis, and severe left main coronary ostial obstruction as described above (Fig 5). Echocardiogram after 3 months showed a gradient of 30 mm Hg from left ventricle to aorta and good relief of the coronary artery obstruction.

Comment

This technique is simple and needs no prosthetic material. Most importantly, it symmetrically enlarges the aortic valve mechanism more completely than the technique of Doty, which extends gussets into two of the three sinuses of Valsalva (180 degrees opposite each other) or that of Myers and Waldhausen [2], whose V-Y advancement flaps into the sinuses must be asymmetric to avoid the coronary arteries, possibly distorting the sinuses and valve leaflets. Our method also allows relief of left main coronary obstruction by excision of the stenosing ring flush with the ostium as in patient 2.

Extensive aortic arch mobilization, as in corrective operation for interrupted aortic arch, allows excision of sufficient abnormal tissue to permit primary anastomosis. This should grow like the aortic anastomosis after coarctation resection and end-to-end anastomosis, or arterial switch for transposition. The extent of ascending aorta

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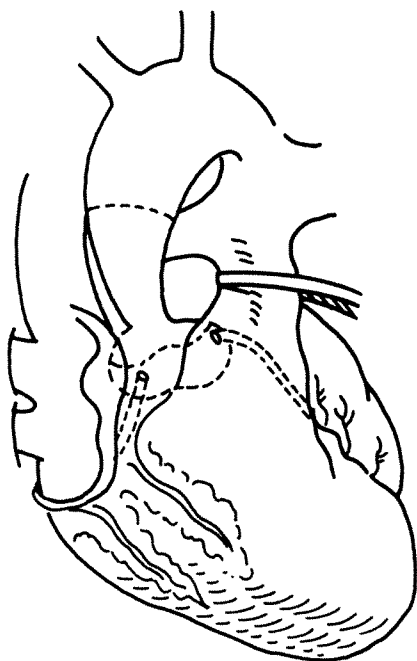


Fig 1. Surgeon's view of the mobilized great vessels and supra-valvar aortic stenosis, showing lines of excision (---).

excision might be limited by compression of the left main bronchus or the right pulmonary artery. For longer stenoses a standard patch technique or excision with patch supplementation would allow symmetrical correction of the deformity.

Long-term follow-up of this lesion after surgical correction using patch aortoplasty techniques has demonstrated good symptomatic results. Few hemodynamic data are

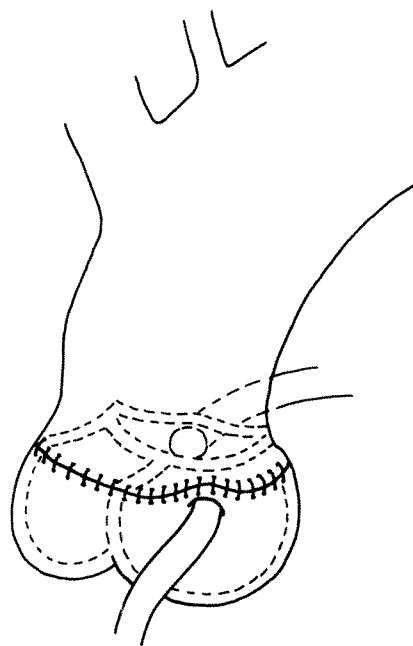


Fig 3. After anastomosis of the normal-diameter ascending aorta to the aortic root.

available, although Keane and associates [3] demonstrated residual gradients ranging from 4 to 55 mm Hg with a mean of 27 mm Hg, the more severe predominantly valvar or subvalvar. Flaker and colleagues [4] reported 8 patients among whom, after patch aortoplasty, 4 had aortic transvalvular gradients between 23 and 48 mm Hg and 2 had serious aortic regurgitation but none had serious supra-valvar gradients. These residual gradi-

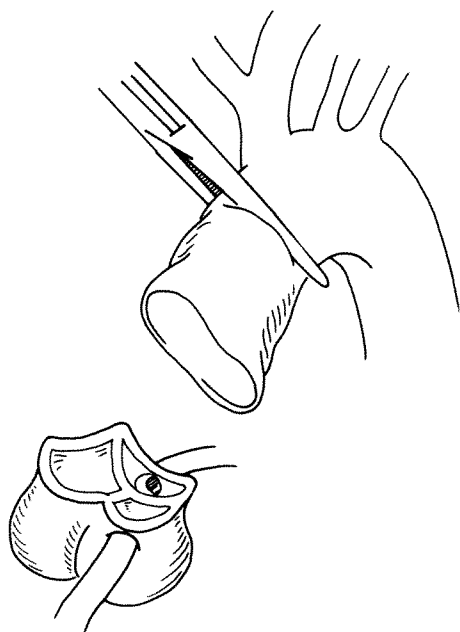


Fig 2. After excision of the stenosing ring, upper half of sinuses of Valsalva, and stenosed segment.

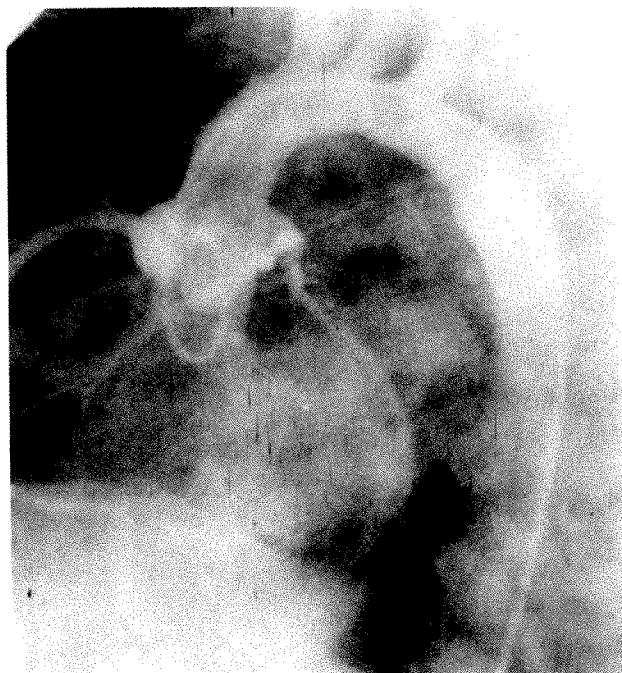


Fig 4. Aortogram after repair in patient 1.

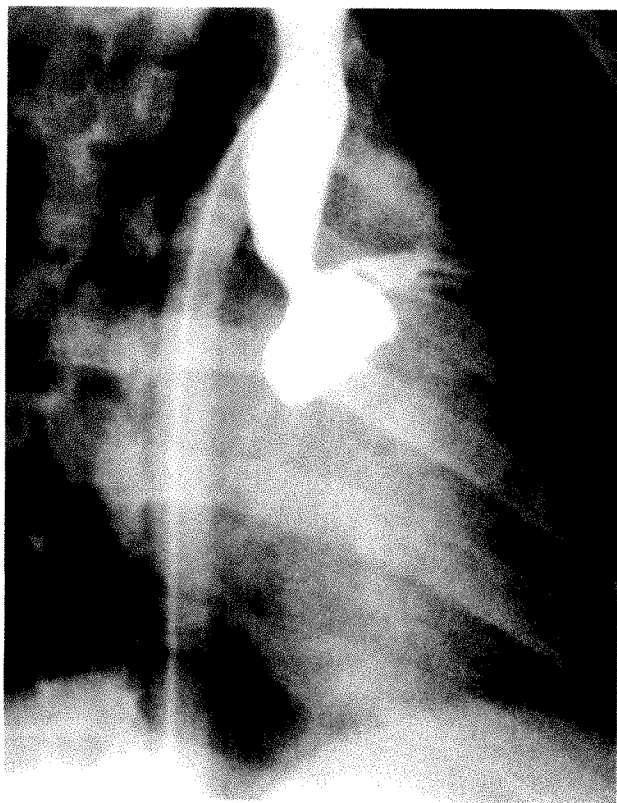


Fig 5. Aortogram of patient 2 showing tight left main coronary obstruction.

ents and regurgitation probably represent incomplete correction of the deformity.

Myers and Waldhausen [2], in 13 patients, had echocardiographic gradients of 25 to 40 mm Hg in their bifurcated patch repair group and less than 25 mm Hg in the V-Y flap repair group. It should be noted that echocardiography tends to overestimate the severity of gradients in this context [2].

The patch technique can also lead to adhesion of the noncoronary leaflet to the patch, leading to acquired bicuspid aortic valve and severe aortic regurgitation (Van Praagh R; personal communication, April 1992).

This new, safe, simple, and effective technique is recommended as providing the best possible relief of all components of this uncommon lesion.

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Transseptal Insertion of Left Atrial Line: A Simple and Safe Technique

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The widespread use of left atrial lines underscores the importance of left atrial pressure monitoring in open heart operations. We present a simple and safe method of intraoperative insertion of a left atrial line during an open heart operation. Foremost among the several advantages of this method is that there would no longer be any concern of postoperative bleeding after removal of the left atrial line.

(*Ann Thorac Surg* 1993;55:785-6)

Monitoring of left atrial pressure has an important application after reparative procedures on the mitral valve, after surgical correction of complex congenital cardiac malformations, in operations for ischemic heart disease with left ventricular dysfunction, and during difficulty in weaning from cardiopulmonary bypass. It is an invaluable aid in the management of critically ill patients in the perioperative period after a cardiac operation until the hemodynamic status of the patient has stabilized. Several routes of insertion of the left atrial line have been described. These include insertion through the left atrial suture line, through the right superior pulmonary vein, and through the left atrial appendage. In all these situations, despite several precautions, the surgeon is always concerned about the possibility of bleeding from the puncture site in the postoperative period after removal of the left atrial line. It is not uncommon to delay the removal of chest drains until the left atrial line has been removed to facilitate the early detection of such bleeding. We present here a simple, convenient, and safe method of left atrial line insertion with virtually no possibility of bleeding after left atrial line removal.

Procedure

Two central lines are inserted from the neck through the internal jugular vein or from the arm through the median basilic vein. In operative procedures involving opening of the right atrium, the tip of the previously identified (by injecting few mL of saline solution through one of these lines) central line can be easily slipped into the left atrium through the suture line of the patch closure of an atrial

septal defect or direct closure of a persistent foramen ovale (Figs 1, 2).

In operative procedures not involving opening of the right atrium with an intact interatrial septum; a small atriotomy 1 cm in length is made on the right atrium parallel and just anterior to the interatrial groove (Fig 3A). The atriotomy margins are retracted and the bulging fossa ovalis septum visualized. A small stab incision is made in the fossa ovalis septum using the tip of a no. 11 surgical blade, and the previously identified central line is slipped into the left atrium through this incision (Fig 3B). Due care must be taken to make a very small incision on the interatrial septum. The atriotomy is closed by a continuous suture. In the postoperative period, necessary precautions to guard against systemic air embolism, as applicable to any other left atrial line, should be observed. When left atrial pressure monitoring is no longer needed, the left atrial line can be withdrawn by few centimeters such that it slips back across the septum into the right atrium and assumes the position of a regular central line. This can be confirmed by the dark color of the blood and by blood gas analysis of the aspirated blood.

Comment

This method of intraoperative placement of a transseptal left atrial line is essentially a repositioning of the previously placed central line across the septum, into the left atrium, under direct vision. There are several advantages to this method. First, there is no possibility of external bleeding in the postoperative period after removal of the left atrial line. Second, the left atrial line will be coming out through the neck or arm as any other central line depending on the initial site of insertion. Consequently, the inconvenience in the management of a central line coming straight out of the chest wall can be avoided. Third, unlike a pulmonary artery catheter it can be easily placed even in infants. We also believe that with this method, we would not face the rare but unfortunate predicament of a "stuck" left atrial line that cannot be removed easily by the usual methods.

The small opening made in the interatrial septum can be justifiably expected to close within a short period, as demonstrated in studies [1, 2] that have reported follow-up of punctures in the interatrial septum. Similarly, a transient and very minimal shunt across the interatrial septum, although theoretically possible, was never a source of worry to us. The separate atriotomy in the right atrium would not pose any additional hazard of bleeding as this was closed under direct vision. Thus, we believe

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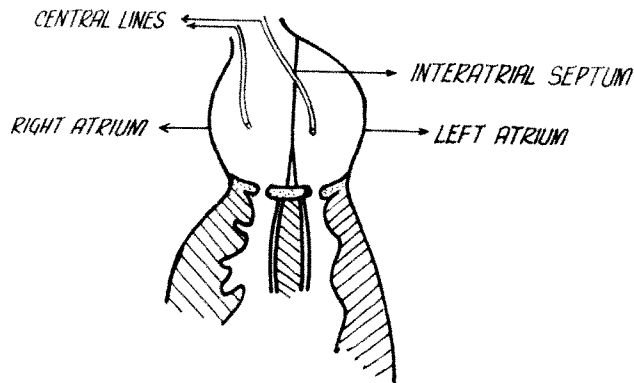


Fig 1. The central line in the right atrium is inserted into the left atrium across the interatrial septum.

that this method of direct transseptal insertion of a left atrial line is a safe, simple, and convenient method of intraoperative insertion of a left atrial line in certain subsets of patients during open heart operations.

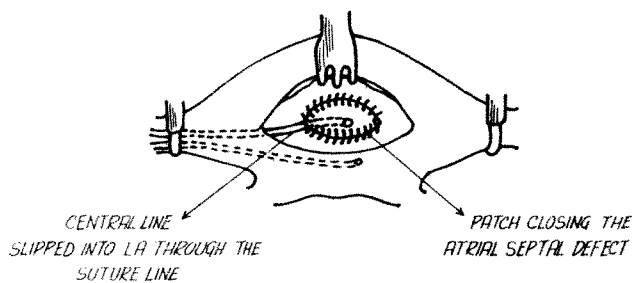
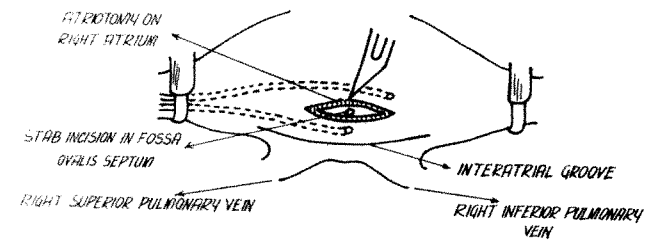
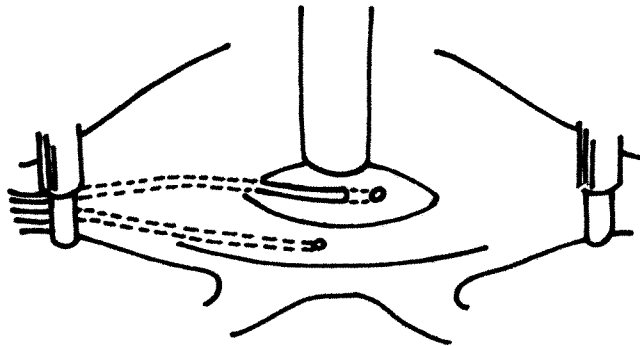


Fig 2. The central line in the right atrium is inserted into the left atrium (LA) across the interatrial septum through the suture line of patch closure of an atrial septal defect.



A



B

Fig 3. (A) A small stab incision is made in the interatrial septum. (B) The previously identified central line is passed into the left atrium through the stab incision made in the interatrial septum.

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Subclavian Artery Cannulation for Infant Extracorporeal Membrane Oxygenation

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A technique is presented for subclavian artery cannulation for extracorporeal membrane oxygenation. This method allows antegrade perfusion of the carotid artery to occur both during extracorporeal membrane oxygenation and after decannulation. This method may prevent neurologic sequelae associated with the more common techniques using the carotid artery.

(*Ann Thorac Surg* 1993;55:787-8)

Extracorporeal membrane oxygenation (ECMO) using venoarterial cannulation is an established form of treatment for a variety of forms of respiratory failure in neonates. The most common technique of vessel cannulation involves using the common carotid artery for arterial inflow and the internal jugular vein for venous return. Neurologic complications have been reported after ECMO, and complications attributable to ligation of the carotid or jugular system [1] are difficult to separate from those neurologic complications that result from intraventricular hemorrhage, cerebral edema, preexisting hypoxia, or other factors related to the ECMO perfusion [2]. These factors have led some authors to now recommend carotid artery and in turn jugular vein reconstruction after ECMO [3]. We have developed a technique (Fig 1) that not only preserves the internal carotid artery after decannulation, but also allows antegrade perfusion through the carotid artery during ECMO.

Technique and Patients

The patient is positioned supine in the newborn intensive care unit and is placed on a shoulder roll, and the head is rotated to the left. A short longitudinal incision is made at the lower anterior border of the sternocleidomastoid border in the right neck. The internal jugular vein is first isolated and mobilized. The subclavian artery is identified and isolated by carefully dissecting the carotid artery and retracting it cephalad. The vertebral artery is identified as the first major branch of the subclavian artery on the right side, and it is ligated. The patient is then heparinized and the ECMO perfusion circuit is prepared for cannulation. Through a longitudinal arteriotomy, the arterial cannula is introduced into the subclavian artery and is advanced through the innominate artery so that the tip of the

cannula will lie just inside the lumen of the aortic arch. An Elecath aortic ECMO cannula (Electro-Catheter Corporation, Rahway, NJ) is used, and sizing of the cannula is based on weight of the infant and anticipated flow rates. In general, an 8F aortic inflow cannula is used for infants weighing between 2 and 3 kg and a 10F for those more than 3 kg. A standard internal jugular venous cannulation is then accomplished through a longitudinal venotomy. An Elecath cannula that is specially designed for venous drainage with multiple side holes is used. The largest venous cannula that can be safely inserted is used, usually a 12F in the average neonate. The catheter is positioned so that the tip lies within the right atrium and the last side hole is positioned opposite the innominate vein to prevent venous hypertension in the contralateral internal jugular vein. The wound is then closed in layers in a standard fashion and the cannulas exit from the upper edge of the incision.

When the child is successfully weaned from ECMO the wound is reopened and the cannulas are removed. Both the vein and the artery are allowed to back-bleed to ensure that no thrombus is present. Preferably, the vein and artery are then both primarily repaired with fine polydioxanone sutures. In general these vessels are closed in a transverse fashion to prevent a localized vessel stenosis. If reconstruction is not possible the vessels can be simply ligated.

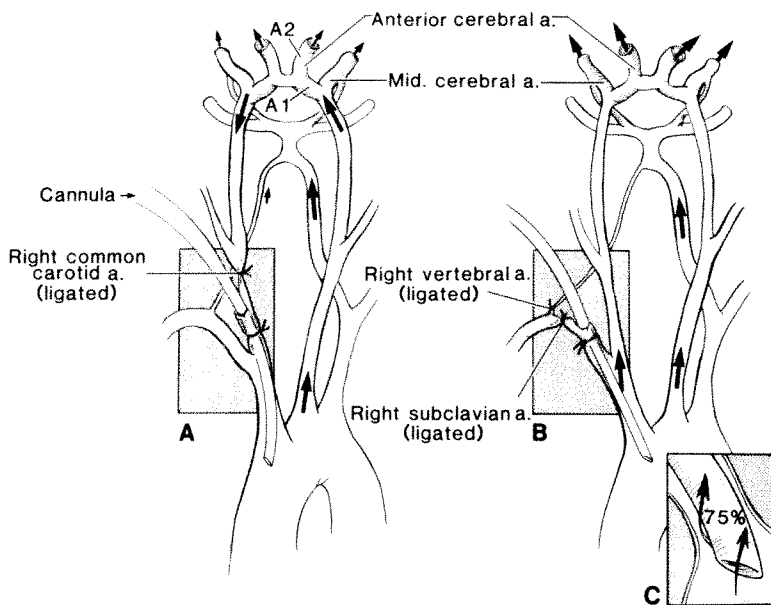
From January 1989 until December 1991, internal jugular to subclavian artery venoarterial cannulation for ECMO has been used exclusively at our institution. A total of 23 patients underwent ECMO using this cannulation technique during this period. Sixteen patients underwent ligation of the subclavian artery at the time of decannulation, and 7 recent patients underwent reconstruction of the subclavian artery at the time of decannulation. All patients were neonates except for 1 patient who underwent ECMO at 29 months of age. The duration of ECMO ranged from 49 to 220 hours (mean, 141 hours).

Transcranial Doppler evaluation of carotid artery flow was done routinely in all patients immediately after the initiation of ECMO, 24 hours after the beginning of ECMO, and 72 hours after decannulation. These transcranial color Doppler studies showed antegrade flow in the carotid artery and A1 segment of the anterior cerebral artery in all patients during ECMO and at 72 hours after discontinuation of ECMO. Antegrade blood flow during ECMO was also seen in the basilar artery of all patients. Retrograde flow was visualized in the right vertebral

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Fig 1. (A) Standard extracorporeal membrane oxygenation cannulation using carotid artery. Ipsilateral internal carotid flow is retrograde through the A1 segment of the anterior cerebral artery. (B) Subclavian extracorporeal membrane oxygenation cannulation preserves antegrade flow in the internal carotid, basilar, and the A1 segment of the anterior cerebral artery. (C) Cannula size that is approximately 75% of the innominate artery size will allow antegrade carotid flow.



artery in 1 patient due to failure to temporarily ligate the right vertebral artery on the ipsilateral side.

Comment

Neurodevelopmental problems in infants after ECMO have been reported in 20% to 35% of patients [1, 2]. The exact cause of these neurologic problems is difficult to isolate, but can be due to intracranial hemorrhage while on ECMO, hypoxic-ischemic encephalopathy, problems related to a carotid ligation, or thromboembolic events during ECMO [1, 2]. Although the exact cause for cerebral dysfunction after ECMO cannot be exactly delineated, the maintenance of antegrade carotid blood flow both during and after ECMO is certainly desirable. The technique we have described preserves antegrade carotid blood flow during ECMO and allows maintenance of antegrade carotid flow after decannulation, even if arterial reconstruction is not technically feasible. Usually the carotid and subclavian vessels in the newborn are quite elastic and it is quite easy to retract these vessels upward and perform this cannulation without difficulty. In our experience, extension of the incision or excessive retraction is not needed to expose the subclavian-innominate arterial junction and perform the cannulation. Although the long-term sequelae of subclavian artery ligation after this technique are not known, long-term problems with subclavian occlusion after subclavian flap arterioplasty or Blalock-Taussig shunts are known and are not severe [4].

It is important in this technique that an arterial cannula that is approximately 75% of the size of the innominate artery is selected so as to allow antegrade carotid flow during ECMO. This can be done by sizing the innominate artery by ultrasound before the institution of ECMO flow. Antegrade flow in the ipsilateral carotid artery was well

demonstrated in this series using the color flow Doppler technique. Other authors have demonstrated abnormal flow velocities in the anterior cerebral vessels after institution of ECMO when the common carotid artery is cannulated [5]. We did not find any flow abnormalities in the anterior cerebral or basilar arteries using this subclavian artery approach. It is important to ligate the vertebral artery on the same side of cannulation, because failure to do so may result in retrograde vertebral flow and the possibility of subclavian steal syndrome.

Although long-term neurologic prognosis may not be different in patients who have carotid cannulation with or without ligation as compared with subclavian artery cannulation, we believe that subclavian artery cannulation offers a unique way to preserve carotid blood flow during and after ECMO. Reconstruction of both the subclavian artery and jugular vein can be done in the majority of patients using these techniques and may prevent long-term neurologic sequelae.

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Quantum Leap Forward in the Management of Cardiac Trauma: The Pioneering Work of Dwight E. Harken

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Doctor Dwight E. Harken made numerous contributions to the field of cardiac surgery, and in particular the management of cardiac missiles. A few highlights are reviewed.

"If . . . history teaches us anything, it is that man in the quest for knowledge and progress, is determined and can not be deterred."

John F. Kennedy, 1962

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FOREIGN BODIES IN, AND IN RELATION TO, THE THORACIC BLOOD VESSELS AND HEART

I. Techniques for Approaching and Removing Foreign Bodies from the Chambers of the Heart

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When compared with the history of surgery in general, the field of cardiac surgery is young, and has evolved almost entirely within the late nineteenth and particularly the twentieth century. This has not been a completely gradual, incremental process. Rather, it has been a time when periods of quiescence have been interspersed with episodes of explosive development, discovery, and initiative. To take the analogy of evolution one step further, this can be regarded as a process similar to "punctuated equilibrium" in which the relatively stable mainstream of cardiac surgery is interrupted with sporadic introductions of new surgical techniques, instrumentation, and technological advances [1]. When viewed within this context, Dwight E. Harken's article entitled "Foreign Bodies in Relation to the Thoracic Blood Vessels and Heart," which was published in 1946, represents a quantum leap forward in the development of cardiac surgery [2]. At a time when progress in cardiac surgery was slow, his contributions to the field inspired an entire generation of younger surgeons, and challenged the establishment to reevaluate its position regarding surgery on the heart. In the words of Blatchford and Anderson [3], Harken's report amounted to a surgical tour de force.

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Background

Interest in penetrating injury to the heart and great vessels precedes recorded history. Hippocrates [4] recognized that cardiac wounds were inevitably lethal, and Aristotle [5] wrote that "the heart alone of all viscera cannot withstand serious injury." The overall pessimism engendered by these founding fathers led to a fatalistic approach to cardiac injuries until well into the eighteenth century. Actually, there had been some thought on the part of Hollerius [6] as early as the sixteenth century that injury to the heart might be survivable. The proof came in 1642 when Wolf [7] noted a healed wound in the heart of a deer and Tourby [8] observed the human equivalent at autopsy in a man who had been stabbed 4 years before his death. Despite these clinical observations, progress in the management of penetrating cardiac injuries did not proceed rapidly. In 1709 Boerhaave [9] reaffirmed the widely held belief that all wounds of the heart were mortal.

In reality, however, data were beginning to accumulate in the experimental work of Block [10] in 1882 and deVecchio [11] in 1895 that suture of cardiac wounds in rabbits and dogs was not only feasible but survivable. This fact was elegantly demonstrated by Rehn [12] in 1896 when he performed the first successful human cardiorrhaphy. Dwight Harken himself noted, with some amusement, that Rehn performed his operation in the same year that Sir Steven Paget commented in his text of surgery, "surgery of the heart has probably reached the limits set by Nature to all Surgery: no new method, and no new discovery can overcome the natural difficulties that attend a wound to the heart" [13]. Harken's commentary on this embarrassing literary overstatement serves as a cautionary note to all students of medicine, ". . . do not make myopic predictions. Furthermore, if you feel you have a great idea, do not parade it until you have reviewed the literature" [14].

The first American to perform cardiorrhaphy was L.L. Hill in 1902. He subsequently reviewed the literature and reported several more cases [15]. Numerous reports of cardiorrhaphy followed. The mortality associated with operative management of these injuries, while still high (approximately 60%), was markedly less than that of nonoperative treatment (approximately 90%).

By the end of the third decade of the twentieth century, several myths relating to cardiac injury had been debunked. All cardiac injuries were not lethal, and the majority of patients who survived for clinical evaluation

were candidates for repair. Bigger [16], however, suggested that pericardiocentesis should be used both diagnostically and therapeutically when possible, with operation being reserved as the treatment for unstable patients. This approach was based on the fact that although the heart and great vessels could be exposed and repaired, in so doing the mortality was high and varied widely. Therapy continued to be reactive rather than anticipatory, and a unified, systematic approach to wounds of the heart and great vessels was lacking. Although cardiorrhaphy was an established technique, it was by no means clear that it was ideal for all cardiac wounds, and in some cases it represented considerable overtreatment.

The Work of Dwight E. Harken

Dwight Harken would soon change the status quo. As a young surgeon in training, he had been intrigued by the muscular strength, valve design, and flow characteristics of the heart. He felt inexorably drawn to study its function further, and in doing so, noted a marked resistance on the part of his mentors to manipulate the heart: "I wondered about the reluctance of these master surgeons to touch it. It seemed incomprehensible that we surgeons who are considerably mechanically oriented should not attack this significantly mechanical organ" [14]. Harken was quite aware, however, that the potential risks of cardiac procedures in the early 1940s were prohibitive, and he confined his ardor for more aggressive cardiac interventions to the laboratory. "To enter this formidable field, I had to find a disease that was absolutely and always fatal. The disease must be positively, absolutely diagnosable, preferably at an early stage; such was subacute bacterial endocarditis" [14]. As a true clinical scientist, he created an animal model of bacterial endocarditis and a cardioscope with which he could look into the beating heart to resect vegetations. Had it not been for the intercession of World War II and the development of penicillin, we would have undoubtedly seen more of this technique.

During World War II Harken was called to duty in the military corps, where he became a consultant thoracic surgeon in the European theater. It was here that he observed shell fragments and other missiles in human hearts. This was a quintessential case of opportunity meeting the prepared mind. Drawing on his prior experience, Harken theorized that foreign bodies should be removed from the heart and great vessels for the following reasons: (1) to prevent embolus of the foreign body or the associated thrombus, (2) to reduce the incidence of bacterial endocarditis, (3) to avoid recurrent pericardial effusions, and (4) to diminish the danger of myocardial damage with subsequent rupture or myocardial aneurysm [2].

In characteristically measured fashion, he consulted with other leading surgeons of the time and discussed these indications. The result was a consensus that the cardiac missiles should be removed. Over a period of 10 months, Harken removed 78 missiles that were within or in proximity to the great vessels. Three of these were embolic. In addition, he extracted 56 foreign bodies from

the heart, 13 of them from the cardiac chambers. Citing the size and location of the missiles as being critical factors in treatment, Harken also categorized foreign bodies that should be left undisturbed. In so doing, he demonstrated the consummate judgment that allowed him to operate on 134 patients without a single death. It is a testament to Harken's surgical intuition that these indications have undergone only modest revision despite the vast changes in the field of cardiac surgery since that time [17]. Several technical aspects that he used then deserve emphasis. First, he routinely opened the pleura at a time when most surgeons were obsessed with extrapleural approaches. Second, every attempt was made to avoid "dislocation" of the heart during manipulation. In addition, the epicardium was kept moist with a procaine hydrochloride solution. Fourth, stitches were placed over the palpated foreign body and were used both to maintain hemostasis during the removal and to secure a pericardial patch later. Finally, the pericardial sac was opened into the pleural space to avoid postoperative cardiac tamponade. These, in addition to numerous other contributions, helped change the field of cardiac surgery and secure Harken's name in surgical history.

Conclusion

When one considers the relative sophistication and technological advancements of the late twentieth century, it is easy to forget the initiatives and developments that have led to the state of cardiac surgery today.

Attribution of credit for great contributions seems to depend on some uneven balance of timing, relevance to current clinical problems, originality, technical skill, and perseverance. As one reviews the rapid development of modern cardiac surgery with these criteria in mind, Dwight Harken's work on "foreign bodies in, and in relation to, the thoracic blood vessels and heart" is truly a landmark in the history of cardiovascular surgery. He was the first to document safe and successful approaches to the removal of cardiac foreign bodies. Moreover, Dr Harken broke down many of the boundaries of fear surrounding the practice of surgery on the heart, thereby laying the groundwork for the many other subsequent developments in cardiac surgery.

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Notice From the American Board of Thoracic Surgery

The American Board of Thoracic Surgery began its recertification process in 1984. Diplomates interested in participating in this examination should maintain a documented list of the operations they performed during the year prior to application for recertification. This practice review should consist of 1 year's consecutive major operative experiences. (If more than 100 cases occur in 1 year, only 100 need to be listed.) They should also keep a record of their attendance at approved postgraduate medical education activities for the 2 years prior to application. A minimum of 100 hours of approved CME activity is required.

In place of a cognitive examination, candidates for recertification will be required to complete both the general thoracic and cardiac portions of the SESATS IV syllabus (Self-Education/Self-Assessment in Thoracic Surgery). It is not necessary for candidates to purchase

SESATS IV booklets prior to applying for recertification. SESATS IV booklets will be forwarded to candidates after their applications have been accepted.

Diplomates whose 10-year certificates will expire in 1995 may begin the recertification process in 1993. This new certificate will be dated 10 years from the time of expiration of the original certificate. Recertification is also open to any diplomate with an unlimited certificate and will in no way affect the validity of the original certificate.

The deadline for submission of applications is May 1, 1993. A recertification brochure outlining the rules and requirements for recertification in thoracic surgery is available upon request from the American Board of Thoracic Surgery, One Rotary Center, Suite 803, Evanston, IL 60201.

Technical Advances in the Treatment of Left Ventricular Aneurysm

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The resulting abnormal geometry after surgical treatment of left ventricular aneurysm has concerned a number of surgeons since the first successful repair in 1958, but little attention was placed on the altered geometry until attempts were made to effect a more physiologic aneurysmorrhaphy in 1973. Substantial attention was focused on a concept of geometric reconstruction from within the left ventricle in 1985. A prosthetic patch was employed with the concept to redirect normal muscle bundles to their original orientation and position. Further refinements include use of improved materials for the repair, preservation and bypass of the left anterior descending coronary artery, ablation of ventricular arrhythmias when indicated, and the absence of prosthetic material

used in contact with the pericardial surface. Our experience with repair of 61 left ventricular aneurysms at West Jefferson Medical Center over a 4½-year period with a 3.3% mortality rate has prompted a change from the standard linear repair to routine use of a modified endoventricular repair. Currently, the low surgical risk due to advances in left ventricular aneurysmorrhaphy combined with the knowledge that contractile areas will progressively deteriorate in ventricles stressed by poor hemodynamics and with data showing improved left ventricular function postoperatively have led to more liberal recommendations for early left ventricular aneurysm repair.

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Patients with left ventricular (LV) aneurysms that occur after myocardial infarction do not form a homogeneous population. The actual incidence depends upon one's definition of LV aneurysm. In this review, the definition of LV aneurysm is that of a postinfarction aneurysm of the left ventricle that is a consequence of transmural scar with dyskinesia (paradox) of the LV motion. The entity occurs in 10% to 35% of patients who have had a transmural myocardial infarction. Schlichter and co-workers [1] reviewed pathologically proven LV aneurysms and found that the natural history involved a 27% survival at 3 years and a 12% survival at 5 years. Proudfit [2] reviewed angiographically proven LV aneurysms and found a natural history that involved a 5-year survival of 47% and 10-year survival of 18%. The difficulty with the definition of LV aneurysm in the literature is evidenced by the variation in the survival of patients with LV aneurysm; the most favorable report of patients treated nonsurgically showed a 5-year survival as high as 70% [3].

The adverse effects of LV aneurysms depend upon the extent of muscle damage, the size of the dyskinetic area, presence of clot, arrhythmias, the extent of coronary disease, and the amount and functional quality of the remaining LV muscle. The results of surgical repair are related to the magnitude of the geometric effects on the remaining left ventricle. These adverse geometric effects are not only secondary to the loss of contractile tissue in the area of the aneurysm but are due to the increase in LV size and volume. The increase in the size of the LV cavity

increases wall stress and increases myocardial oxygen demand as dictated by Laplace's law. Using Mirsky's [4] modification of Laplace's law, the largest cross-sectional wall tension at the equator of the ventricle or circumferential wall stress may be calculated. Circumferential wall stress and thus the myocardial oxygen consumption are found directly proportional to LV dimensions. Evolution of the principles of LV aneurysm repair now make it mandatory to correct not only the mechanical problem secondary to the failed cardiac physiology but also the atherosclerotic lesions resulting in ischemia of the remaining functional areas of the heart.

Indications for Operation

Congestive Heart Failure

The reasoning offered for surgical repair of LV aneurysms that result in congestive heart failure is based on the principles outlined in the previous paragraph. There may be an additive effect of ischemia secondary to coronary atherosclerotic lesions in the remaining coronary vessels.

Emboli

Another clear indication for repair of LV aneurysms is systemic arterial emboli, many of which may be "silent." One half of patients with LV aneurysms who undergo operation or autopsy have mural thrombi [1, 5]. It is our contention that when transmural infarction has resulted in stasis and endocardial injury with the formation of irregular mural thrombi, there is rarely, if ever, a true healing with fibrosis or neoendocardium over such thrombi.

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Arrhythmia

When myocardial ischemia coexists with ventricular irritability, patients with an LV aneurysm may have development of automatic ventricular arrhythmias. A reentrant rhythm may occur when two or more electrically heterogeneous pathways are connected proximally and distally. An impulse arriving at a distal connection may return by the initially blocked pathway. If the originally blocked site recovers excitability, the impulse may reenter the circuit. Operative excision is a therapeutic option for a reentrant ventricular tachycardia. Patients with ventricular arrhythmias and coexistent ventricular aneurysms are candidates for mapping and excision of the reentrant circuit at the time of ventricular aneurysm repair. Programmed electrical stimulation at the time of cardiac catheterization identifies sustained ventricular tachycardia as life-threatening. The responsible ventricular tissue can be identified [6].

There is controversy concerning the necessity of studying with pharmacologic testing and mapping all patients who have ventricular aneurysms. There is a definite trend at this time to perform such preoperative testing because such a large number of people in this country have postmyocardial infarction "sudden death."

Angina

The myocardial ischemia in the patient with an LV aneurysm is aggravated by increased wall tension. Angina may be the major symptom in a patient with an isolated ventricular aneurysm when the oxygen demand exceeds its supply. According to Wynne and associates [7], a periischemic "border zone" with weak contractions has been described surrounding the nonischemic muscle.

Concomitant atherosclerosis in the coronary arteries of noninfarcted myocardial bed will accentuate the degree of angina.

Size and Rupture

Even though aneurysms may progress to an enormous size, frank rupture of an established aneurysm is rare. As a homeostatic defense mechanism, the body calcifies the area of paradox. Occasionally, the aneurysm may expand and progress to erode through the diaphragm or into pulmonary structures. Other factors permitting, a large aneurysm is an indication for operation.

Mitral Insufficiency

Mitral valve regurgitation in association with an LV aneurysm—an unwelcome finding even when standing alone—carries a significant increase in operative mortality if secondary to papillary muscle involvement by the infarction [8]. Rarely will an associated coronary revascularization reverse mitral valve insufficiency secondary to scarred papillary muscles in these patients. Valve repair or replacement can often be accomplished through the opened ventriculotomy used for aneurysmorrhaphy.

Impairment of Nonaneurysmal Myocardium

The *global* ejection fraction is a standard method used to numerically quantify the ability of the heart to eject.

However, the *contractile* ejection fraction of the noninfarcted area of a heart with an LV aneurysm is more useful, because it evaluates the function of the nonaneurysmal muscle mass. The presence of an LV aneurysm, especially involving more than 25% of the LV surface, burdens nonaneurysmal myocardial fibers and ultimately decreases the contractile ejection fraction. This phenomenon of LV stress is not too dissimilar from the problem of aortic valvular insufficiency, in which patients are seen to change from an acceptable ejection fraction with an acceptable operative mortality to an inordinately low ejection fraction with an almost prohibitive operative mortality within a time frame of as little as 1 year. Although some authors have advised repair of LV aneurysms only if medical measures fail [9, 10], a more current understanding of the pathophysiology has led clinicians to advise repair before such "irreversible changes," secondary to progressive impairment of nonaneurysmal muscle by increased wall tension, if an acceptable mortality rate can be achieved by the surgical team [11].

Anatomical and Physiological Notes

The normal heart has an elaborate architecture with fibers and muscle layers moving in different directions. The formation of an LV aneurysm distends and enlarges the ventricular cavity, grossly distorting the directions of the muscle fibers. In the presence of an aneurysm, the aneurysmal area of the ventricle expands during systolic contraction. A portion of the forward flow stroke volume is actually "stolen" when an LV aneurysm involves more than 10% of the ventricular surface, causing shortening limits of the remaining myocardial fiber to be exceeded. The ventricle dilates and stiffens, stroke volume decreases, and the end-diastolic pressure increases [12] (Fig 1).

With enlargement of the LV cavity, tangential pressures on the heart wall must be higher to exert acceptable arterial blood pressure. The surgeon, ideally, should attempt to reshape the LV cavity in such a way that muscle bundles are brought toward their original orientation (Table 1).

Treatment

In 1881 the cause of LV aneurysm was determined to be secondary to myocardial infarction [13]. By 1922, LV aneurysms were identified by roentgenography [14], but not until 1951 could an LV aneurysm be diagnosed angiographically [15]. Treatment of LV aneurysm has classically included medical therapy, surgical repair, and cardiac transplantation. Small aneurysms with no clot and no elevation of the LV end-diastolic pressure should be followed up medically with noninvasive techniques if the patient is asymptomatic. Aneurysms may become quite large as they "mature" after myocardial infarction. However, in our experience, there is no aneurysm that is "too large," especially if the patient does not have mitral insufficiency. If the papillary muscles are not involved, there is always "enough remaining ventricle" to sustain

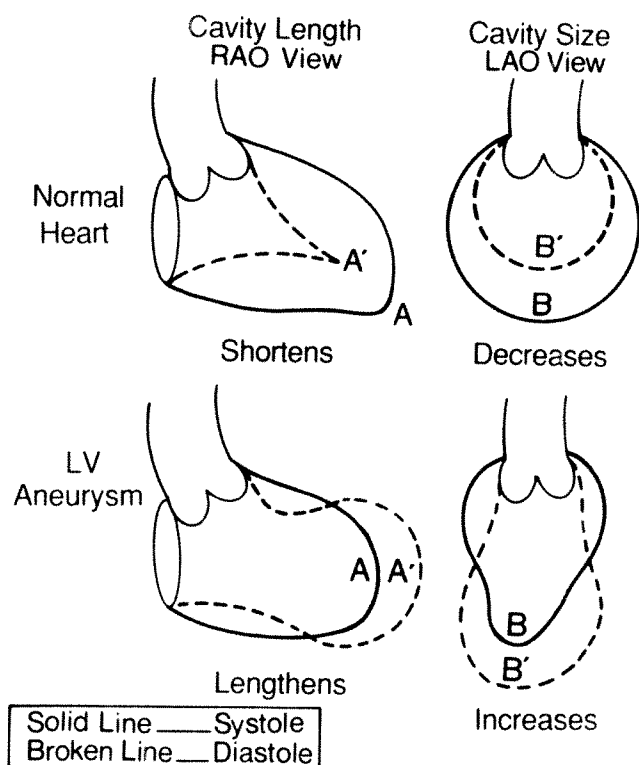


Fig 1. Left ventricular (LV) function in systole and diastole of the normal heart and the heart with LV aneurysm. Note the LV cavity length (A to A') shortens and the size (B and B') decreases with systole. When an LV aneurysm has developed, the cavity length (A to A') and size (B to B') increase during systole. (LAO = left anterior oblique; RAO = right anterior oblique.)

adequate cardiac output, and even hearts with massive aneurysms may be surgically repaired [8]. Patients with asymptomatic moderate-sized LV aneurysms with a global ejection fraction of 0.55 or greater and a normal contractile ejection fraction may be treated medically if the patient has no serious coronary disease. However, when the contractile ejection fraction is less than 0.50, the risk of deterioration is great and the patient should be considered for operation unless the aneurysm is small. Even with more extensive LV damage, many seemingly "hopeless" cases may be successfully treated with aneurysm repair when the contractile ejection fraction is 0.25 to 0.30 if the mean pulmonary artery pressure is less than

Table 1. Effects of Left Ventricular Aneurysm

% Ventricle Involved	Clinical Effect
10%	Decreased ejection fraction
15%	Increased LVED pressure, increased LVED volume
20%	Left ventricular enlargement
25%	CHF
>25%	Myocardial fiber shortening limits are exceeded
40%	Shock

CHF = congestive heart failure; LVED = left ventricular end-diastolic.

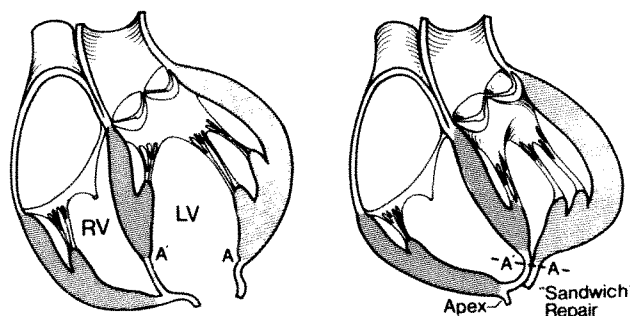


Fig 2. Standard linear ("sandwich") repair of a left ventricular aneurysm where point A is sutured to point A' to a variable distance on the ventricular septum. The geometry of the heart is inappropriately reconstructed as the remaining functioning left ventricular cavity is reduced in size and the lateral wall and medial (septal) wall are sutured together at a point that they would normally be separated by several centimeters. The left anterior descending coronary artery is occluded by sutures. (LV = left ventricle; RV = right ventricle.)

40 mm Hg and the cardiac index is greater than or equal to $2.1 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ [11]. If there is an associated cardiomyopathy due to a cause other than ischemia, a poor outcome may be expected. Clearly, transplantation should be performed as a treatment of choice when the contractile ejection fraction is less than 0.25 and when there is right ventricular dysfunction, permanent mitral insufficiency, and poor target coronary arteries for bypass.

Repair of Left Ventricular Aneurysm

In 1944, Beck [16] described his attempt to plicate ventricular aneurysm using fascia lata. Modern surgical treatment, however, has been attributed to Likoff and Bailey [17], who in 1955 performed a closed resection of an LV aneurysm using a special side-biting clamp through a thoracotomy incision.

Linear Repair

In 1958, Cooley and colleagues [18], using cardiopulmonary bypass, performed the first successful aneurysmectomy using a buttressed linear suture line. This "standard linear repair" is still the most common repair used today (Fig 2). A linear repair of the heart is usually carried out using felt strip buttresses to "sandwich" the closure as a leak-proof repair.

A primary closure with sutures through the fibrous base of the aneurysm, and closure using absorbable polyglycolic acid strips to reinforce the linear repair, are modifications of that technique. Each avoids the use of prosthetic material on the surface of the heart which may become infected, erode into pulmonary structures, or present technical problems if reoperation is necessary. A major disadvantage of this conventional repair is that the lateral and medial (septal) wall of the left ventricle are sutured together at a point where they would naturally lie several centimeters apart, thereby significantly decreasing the functional LV cavity size and distorting the natural LV

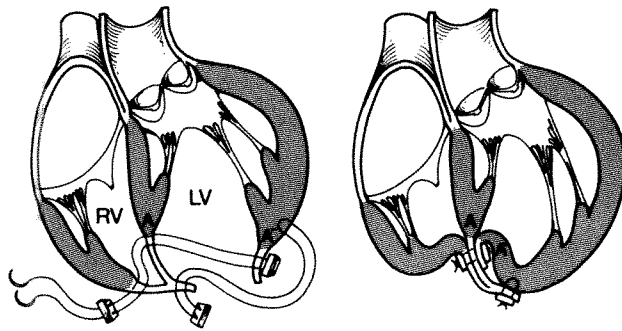


Fig 3. The Stoney repair of left ventricular aneurysm was an early attempt to increase the curvature of the ventricular segments. The lateral myocardial wall is advanced down the ventricular septum to the junction of scar and healthy muscle. (LV = left ventricle; RV = right ventricle.)

geometry (see Fig 2). There is no exclusion of septal paradox when the septal area is significantly involved.

Plication

Generally, cardiac surgeons plicate ventricular aneurysms during cardiopulmonary bypass in association with coronary artery grafting when considerably less overt scar than was anticipated from preoperative angiograms is found at the time of operation. In one study, plication was a factor that did not significantly affect long-term survival of patients after aneurysm repair [19]. Generally, plications are reserved for small scars in patients who do not have serious LV dysfunction and elevation of the LV end-diastolic pressure. One real hazard of using the technique of plication is that of missing an intraventricular clot attached to the endocardium and causing its embolization by the plicating sutures.

Geometric Reconstruction: Early Attempts

Hutchins and Brawley [20], in 1980, reported 18 patients who died after repair of ventricular aneurysms. In studying the human left ventricles, a method for estimating ventricular functional activity of the heart at autopsy was described by applying a modification of Laplace's law. A curvature thickness index correlated with the pressure-producing activity of the heart was used to study the influence of cardiac geometry on the results of operation. Hutchins and Brawley noted that reduced curvature thickness indexes in patients with postoperative shock appeared to arise as a result of ventricular reconstruction that reduced ventricular wall curvature. This important study was the first to suggest that LV function after LV aneurysm resection could be improved by altering the standard repair to a more favorable geometry. Hutchins and Brawley specifically noted that the repair for LV aneurysm, as described by Stoney and associates [21], was preferable as it increased the curvature of the ventricular segments. The repairs by the Nashville group were carried out by advancing the lateral myocardial wall down the ventricular septum to healthy myocardium (Fig 3). They noted an improvement in the LV end-diastolic pressure in 50% of patients. Adequate size of the remain-

ing ventricular cavities and clinical improvement in the majority of the 29 patients were also reported. Stoney and associates did specifically comment that no attempt was made to revascularize the left anterior descending coronary artery.

Daggett and associates [22] also were troubled by deformity of the ventricular cavity. The introduction of their external patch technique for ventricular reconstruction in patients undergoing inferior wall infarctectomy was another milestone in the surgical treatment of LV aneurysms. Komeda and associates [23] reported their early work, which began in 1982, of using an "inverted T closure" of the left ventriculotomy as an attempt to restore a more normal conical shape to the left ventricle. The operative mortality was statistically less than that of conventional repair ($p < 0.01$). However, the "inverted T closure" patients were operated on later in the study when the team had more experience and their overall surgical technique had improved (Fig 4).

Endoventricular Repair

Jatene [24], in 1985, introduced the concept of geometric reconstruction of the left ventricle using prosthetic patch material. Ventricular dysfunction after "sandwich" repair of ventricular aneurysms with Teflon felt strips had been found by his group to lead to varying degrees of ventricular dysfunction. He noted the maldirection of normal spiral muscle bundles after infarction and ventricular aneurysm formation with bundle distortion in the transverse as well as longitudinal direction [5]. His theory is to redirect the normal muscle bundles as much as possible to their original position and orientation to induce a reduction of the ventricular diameter and a shortening of the ventricular cavity in systole. The basic concept is to reshape the LV cavity in such a way that it resembles an

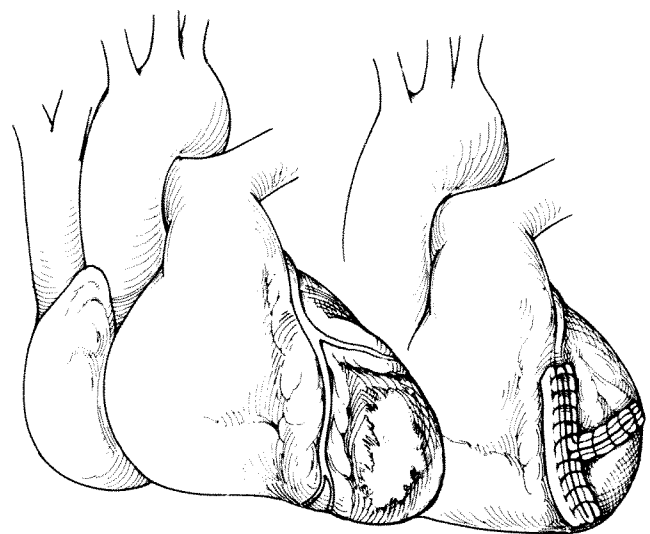


Fig 4. Inverted T closure of left ventricular aneurysm has been reported in an attempt to restore a more conical shape to the left ventricle. Buttressed sutures are used and the left anterior descending coronary artery is included in the suture line.

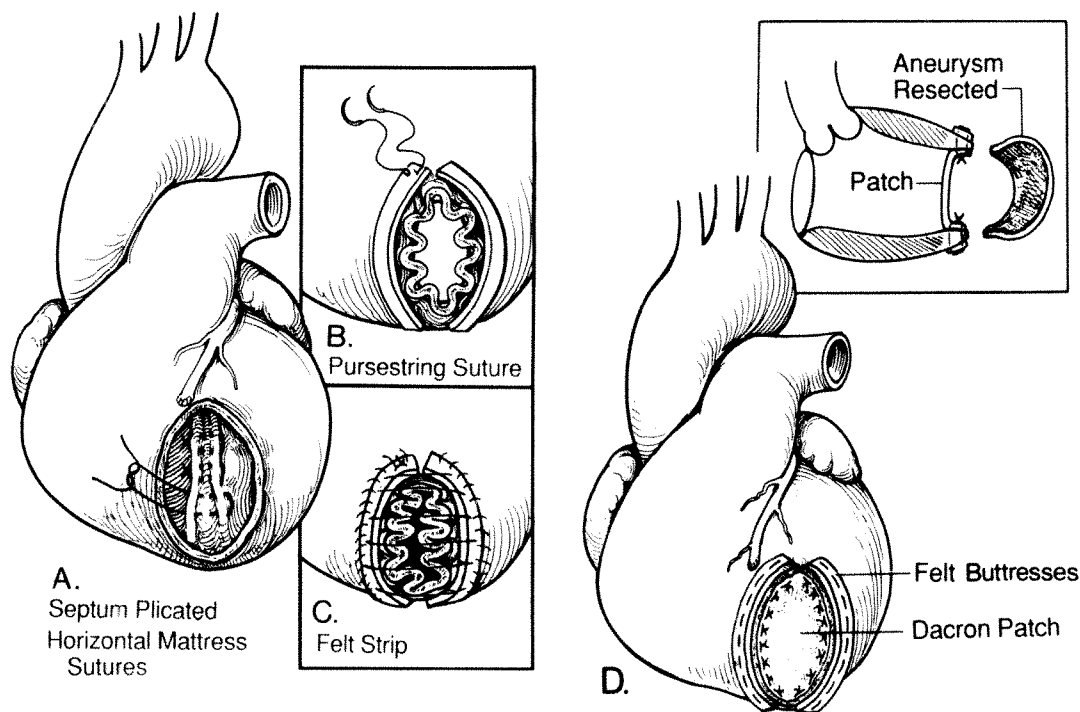


Fig 5. Jatene techniques (endoventricular circular plasty): (A) Septal distortion or bulge is first addressed by plication with horizontal sutures. (B) The aneurysmal mouth is circumferentially constricted by pursestring suturing to avoid the distorted geometry of a linear repair. (C) Prosthetic material is used to oversew this area. (D) When the aneurysm is large, and direct suture would produce inordinate ventricular distortion or suture tension, a Dacron patch is sutured to the mouth of the aneurysm. These techniques leave considerable material exposed to the pericardial cavity.

infarcted left ventricle in which distention of the infarcted area did not occur. Palpation of the myocardial thickness is used to identify the area to be obliterated. The first step in Jatene's technique is to tailor the left ventricle toward an oval cavity. This is carried out by placing one or two pursestring sutures at the transition from normal to fibrous tissue on a beating heart. The pursestring sutures are placed around the orifice of the aneurysm so that the orifice can be brought down to a size estimated to be close to that of the original infarcted area of left ventricle. Septal dysfunction is also addressed by a septal plication. The concept is to prevent an elongation of the orifice with approximation of the fibrous rim as occurs in the standard linear repair. A direct suturing of the aneurysm is then carried out if the size seems adequate. If not, a ventricular patch is used to complement the closure (Fig 5). It is this accomplished surgeon's opinion that operating with the heart beating makes it much easier to decide on proper suture placement. The Jatene technique, however, involves a sizable amount of prosthetic patch material and felt surface strips that reinforce the margins of the repair, all of which are exposed to the pericardial cavity. A postoperative infection of such material from a sternal infection or otherwise will present a formidable problem. Adhesions from external prosthetic material are troublesome should reoperative coronary artery bypass grafting ever become necessary. Hospital mortality was decreased from 11.6% to 5.8% after changing to his current technique of LV reconstruction.

Dor and associates [25], since 1984, have used circular patch techniques for LV reconstruction and have named their techniques "endoventricular circular plasty." Like Jatene's technique, the septal akinesis, as well as the remaining paradox of the left ventricle, is excluded. The methods of repair used by Dor's group have been reported to result in superior hemodynamics [11, 26]. Left ventricular reconstruction is carried out using a pericardium-covered Dacron patch. A more complex operation may be performed, wherein an endocardial flap of scar, which is hinged on the septum, is mobilized with a 3- to 4-cm radius. It is then sutured superiorly, laterally, and inferiorly. The left anterior descending coronary artery is spared and is bypassed whenever possible. A distinct disadvantage of the technique is that the repair, which is buttressed with felt, is left open. A circular suture is necessarily placed around the margins of the cut ventricle to control bleeding. A theoretical disadvantage of the endoventricular flap technique is that the flap, which is fashioned of scarred myocardium, may develop paradox in the late postoperative period. The patient follow-up with that method has only been approximately 1 year. Although the concept of having an autogenous lining for the left ventricle is appealing, emboli from prosthetic LV patches have not been reported (Fig 6). More recent experience with 207 patients and a 6.2% mortality was reported by Dor and associates [26] at the 72nd Annual Meeting of the American Association for Thoracic Surgery in Los Angeles on April 24, 1992. Uncertainties were

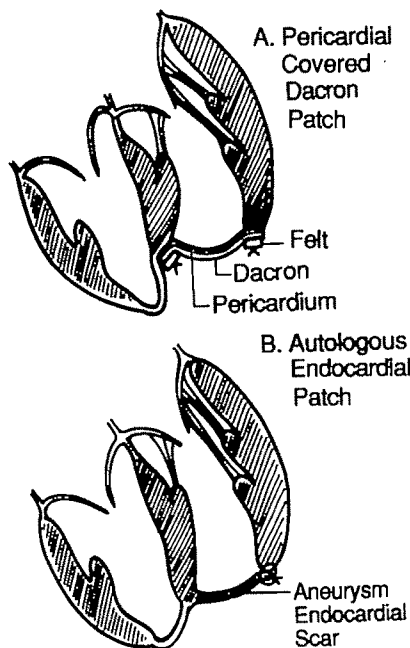


Fig 6. Dor techniques (endoventricular circular plasty): (A) A Dacron patch lined with pericardium is sutured circumferentially at the junction of scar and normal muscle. The excess lateral aneurysm is excised, and the repair is left open. (B) Autologous endocardial patch technique. Reconstruction is carried out by developing a septal hinged flap of scar that is then sutured circumferentially around the remaining mouth of the aneurysm.

mentioned concerning size of the patch, quality of the patch, and mitral insufficiency. Dor and associates concluded that their technique is feasible for LV aneurysm in any location, that it excludes all akinetic areas, and that it improves LV function to a stage that exceeds the theoretical contractile ejection fraction.

The endoventricular technique described by Cooley [27] is simplified by no excision of aneurysm tissue and by the use of an elliptical woven Dacron patch sutured to the inside of the left ventricle at the proper area as described by Jatene and Dor. His repair is called "ventricular endoaneurysmorrhaphy." The left ventricular closure on the surface of the heart was initially carried out using polyester felt strips for reinforcement. An intervening cavity that fills with clot is allowed to occur. Both Dor and associates [26] and Cooley [28] have abandoned the technique of allowing prosthetic material to remain in contact with the pericardial cavity. Komeda and associates [23] mentioned the use of autologous pericardium or a glutaraldehyde-preserved bovine pericardium for repair of acute LV aneurysms and have reserved Dacron graft material for chronic LV aneurysms. The difficulty with suturing Dacron graft is mentioned in their report. The long-term effects of pericardium subjected to LV pressure is unknown. Endoventricular patch repair achieved a statistically significant survival over conventional repairs in patients with severe LV impairment (ejection fraction < 0.20).

Endoventricular Repair With Felt Patch

We have modified the above-mentioned techniques, yet maintaining the basic geometric philosophy that improves LV function. After lysing adhesions, opening and decompressing the LV, and carefully removing any thrombus, we bypass coronary arteries. Cold fibrillation to 25°C is preferred to cardioplegia if there is no major LV hypertrophy or aortic insufficiency upon manipulation of the heart. The heart is defibrillated temporarily every 20 minutes. A thick nonporous Teflon (USCI, Division of Bard Cardiovascular, Inc, Billerica, MA) felt oval patch that has been soaked in antibiotic solution is used for the endoventricular repair as it conforms more readily and securely than stiff Dacron patch material to the irregular trabeculated endocardial surface of the left ventricle. Usually, some resection of dense trabeculae at the muscular-scar junction is required to allow a smoother coaptation between the patch and ventricle. The patch material has a velour-like surface, which enhances a firm attachment of fibrous tissue and neoendocardium. Continuous 2-0 polypropylene over and over suture is used to suture the patch to the "mouth" of the aneurysm. The suture line is interrupted at three to four points, as a tear anywhere along the course of a solitary suture line would likely result in failure of the repair. The surface of the heart is then closed with a continuous double-run polypropylene suture without any foreign material exposed to the pericardial cavity. The left anterior descending coronary artery (LAD) is spared and bypassed whenever possible to afford some degree of increased blood supply to the upper septal areas and diagonal branches (Fig 7). For repair of posterior ventricular aneurysms, the technique is essentially the same except that the patch is triangular rather than oval. Not only can arrhythmogenic endocardial foci and scar be excised, but also the mitral valve may have a concomitant annuloplasty procedure or replacement when indicated. The advantages of this modification are as follows:

1. LAD is preserved and can be bypassed.
2. Thick felt readily conforms to the irregular LV trabeculated wall.
3. Felt is considerably easier to suture than stiff woven Dacron.
4. No prosthetic material is in contact with the pericardial surface.
5. Favorable LV geometry is maintained.
6. Covering (neoendocardium) on LV felt patch has been tested and proven secure by use in prior cardiac procedures.

There has been one report of an experiment on 6 domestic pigs in which a Dacron patch was inserted to simulate an LV anterior apical aneurysm. The authors of that report concluded that patch ventriculoplasty was of no greater benefit than linear repair [29]. The work was refuted in a letter to the editor by Dor and co-workers [30], in which they pointed out that the experimental model cannot be compared with postinfarction LV aneurysms in humans because such patients have a slow change in

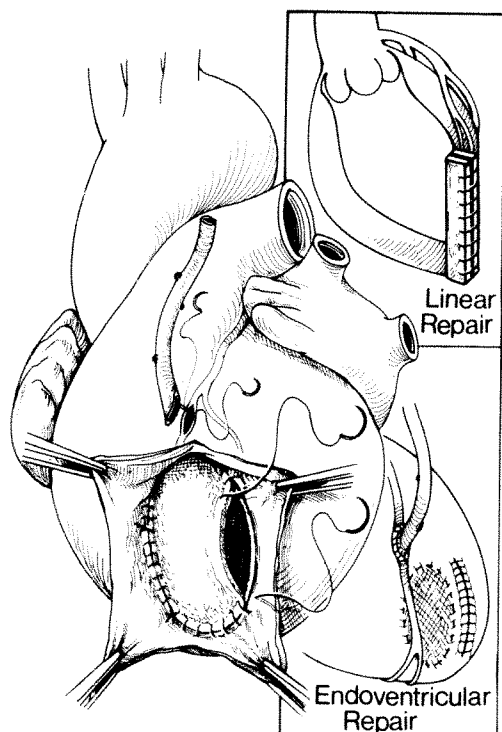


Fig 7. Modified endoventricular repair of a left ventricular aneurysm: After removal of the clot and, if necessary, excision of irritable foci, an oval endoventricular Teflon felt patch is sutured at the "red/white junction" circumferentially around the mouth of the aneurysm with 2-0 polypropylene continuous suture. The appropriate geometry of the heart is maintained as opposed to use of the linear "sandwich" repair. Patch size is determined using the size of the mouth of the aneurysm and the degree of left ventricular dilatation as guidelines. The size of the patch approximates the size of the left ventricular infarcted area if dilatation, paradox, and aneurysm did not occur. Septal paradox is relieved with this technique, as opposed to the standard linear repair (top insert). As shown in the bottom insert, the ventriculotomy is closed longitudinally without prosthetic material, and clot is allowed to form in the obliterated cavity. A concomitant coronary bypass graft is performed to the left anterior descending coronary artery. There is no felt contact with the pericardial surface.

ventricular global geometry and regional curvature. Increases in LV end-diastolic volume, loss of muscle mass in areas of the infarction, and hypertrophy of the remote myocardium are all secondary changes that occur in patients with left ventricular aneurysm.

Two clinical reports compared linear and endoventricular repair. Cooley [28] studied 24 patients postoperatively after endoventricular repair and found 71% had improved ejection fraction from a mean of 0.277 preoperatively to a mean of 0.368 postoperatively ($p < 0.01$). The outcome for patients who underwent repair by conventional techniques (103 historical controls) were 51% improved, 15% worse, and 26% unchanged. Endoaneurysmorrhaphy resulted in 76% improved, 6% worse, and 18% unchanged.

In a retrospective study flawed by a nonrandom statistically insignificant sample, Kesler and associates [31] compared the effectiveness of linear closure (40 patients)

and circular closure (22 patients) as techniques to repair LV aneurysms. Two-dimensional echocardiograms were available for comparison in 29 linear and 13 circular closure patients postoperatively. The circular technique was performed as described by Jatene. Three of the linear closure group had plications. Ten of 22 patients needed no patch. Kesler and associates observed no significant difference between the two techniques. Analysis of clinical results with three-dimensional evaluation techniques such as multiplane echocardiography, gated computed tomography, or magnetic resonance imaging might have assisted in determining whether differences in function and geometry of the techniques had been present. In any event, the small sample size greatly limits the usefulness of the study.

Skeletal Muscle Reconstruction

In 1966, Petrovsky [32] reported the use of the diaphragm to reinforce LV repairs. A logical extension of this work in light of advances in the field of dynamic cardiomyoplasty was reported in 2 patients by Magovern and associates [33] in 1987. The latissimus dorsi muscles were used to cover large LV aneurysmal defects. They were electrically trained to contract during systole using a dual chambered atrioventricular sequential bipolar pacemaker. Reconstructed fibrous endocardial tissue provided the inner layer of the repair. Both patients improved from congestive heart failure to normal activities. Ejection fractions were improved with stress in both patients in the late postoperative period when the pacers were switched from the off to on mode. Further work is needed to put this operative approach in proper perspective in relation to indications and patient selection (Fig 8). This has also been investigated by Carpentier and associates [34].

Left Anterior Descending Revascularization

Classic techniques using the linear closure of LV aneurysms involve the suturing closed of the LAD for antero-lateral aneurysms, unless some residual aneurysm is left in place. More often than not, bypass to the LAD is feasible in patients with LV aneurysm. In patients with multiple areas of distal LAD atherosclerotic disease the disease has developed simultaneously throughout the LAD and some collateral circulation has usually occurred, offering protection from aneurysm formation with LAD obstruction. This is in contrast to patients who experience a sudden occlusion of a proximal LAD lesion with very little distal LAD disease. An LV aneurysm more often develops in the latter survivors. After studying early and late determinants of survival after LV aneurysm repair, Rizzoli and associates [35], in 1988, insisted on a revascularization of the LAD. A report on LV aneurysms from the Montreal Heart Institute [36] noted a favorable outcome influenced primarily by revascularization of residual territory of the LAD. The authors of that report also emphasized that an improved survival rate with that philosophy was reported by Atkins [37] and by Najafi and co-authors [38]. Cooley [27] mentioned that any resection of aneu-

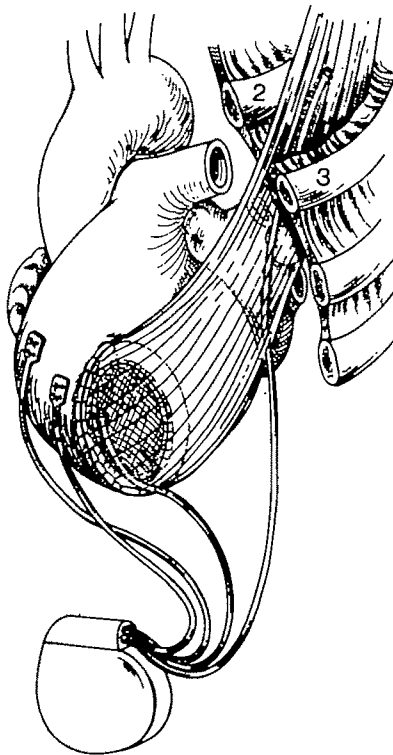


Fig 8. Repair of a large left ventricular aneurysm with a paced left latissimus dorsi through a second rib window. Fibrous endocardial tissue is used as the inner left ventricular lining covered by the muscle flap. A standard atrioventricular sequential bipolar pacemaker is used with the sensing leads implanted on the right side of the heart. The bipolar pacing leads are placed proximally and distally on the latissimus dorsi flap.

rysmal surface should be done on the ventricular free wall side instead of the septal area to avoid suturing or occluding vessels from the LAD in the interventricular septum. Before our change in basic technique, we reported a 5-year survival of 88% in patients undergoing ventricular aneurysm repair who had a concomitant internal mammary artery graft to the LAD. The 5-year survival of patients having a saphenous graft to that vessel was 72%. When no graft was placed to the LAD system in the course of LV aneurysmorrhaphy, the 5-year survival dropped to 65%. Because of the small number of patients, the beneficial effect of internal mammary artery grafting as opposed to saphenous vein grafting could not be statistically demonstrated. Also, there is a tendency among cardiac surgeons to avoid use of the internal mammary artery graft in older, sicker patients in whom the primary objective is to get such patients successfully through what may be a serious operation. Of the overall 246 patients reported, 55% had an LAD graft, indicating a philosophy of offering revascularization to perianeurysm myocardial mass with marginal blood supply to enhance postoperative ventricular function and survival of the early postoperative stress of operation [20]. Theoretically, this approach may decrease postoperative ventricular arrhythmias and has varied from earlier experience as

reported in 1977 [39]. Dor and associates [26], in updating their experience, emphasize use of internal mammary artery grafting (85% of 207 cases) of the LAD in antero-lateral LV aneurysm repair.

Cardiology Center Experience

In the period from July 1, 1987, through December 31, 1991, 61 patients had repair of LV aneurysms on our service at West Jefferson Medical Center. The average age was 56.6 years. There were 44 male and 17 female patients in the group. Concomitant coronary bypass grafts included an average of 3.06 grafts per patient. Fifty-four aneurysms were anterolateral, and there were seven inferior aneurysms in the group. Thirty-five patients had bypass to the LAD in conjunction with their anterolateral aneurysm repair. Internal mammary artery grafts were used in seven instances. Initially endoventricular repair was used only sporadically; however, it has been used in our last 22 consecutive patients.

There were two hospital deaths in the group (3.3%). A 70-year-old woman was transferred to West Jefferson Medical Center in congestive heart failure receiving amiodarone who had ventricular arrhythmias. She had LV aneurysm repair, mitral valve replacement, and coronary artery bypass with an intraaortic balloon pump and died of a low cardiac output syndrome. There has been one death in the last 49 patients (2.0%). That patient, a 42-year-old blind, diabetic man on chronic dialysis with cor bovinum, had a preoperative ejection fraction of less than 0.20 and pulmonary hypertension to 80 mm Hg. He had a ventricular aneurysm repair and three concomitant coronary bypass grafts. After an initially gratifying response, he had sudden death during endotracheal suctioning on the first postoperative day.

Since March 1989, the majority of patients have had preoperative testing for ventricular arrhythmias at the time of cardiac catheterization and, when indicated, excision of irritable foci during the time of aneurysm repair. All patients, except 1 who had preoperative electrophysiological testing, have been studied postoperatively and have had no serious ventricular arrhythmias requiring drug therapy. The 1 patient required an automatic implantable cardioverter defibrillator. There has been one late death secondary to ruptured mitral valve chordae tendineae and chronic pulmonary disease.

There has been considerable change in LV aneurysm surgery since the surgical attempts for treatment of this entity in the early years of cardiac surgery. Mortality rates since 1972 have ranged up to 20% with a mean mortality of $9.4\% \pm 5.2\%$. When combined with other cardiac procedures, the mortality rate ranges up to 23% with a mean of $11\% \pm 5.6\%$ [40]. The statement that aneurysm repair should be carried out only if medical measures fail has been appropriately challenged as cumulative survival rates have been reported. Better postoperative LV function at rest and during exercise has been found in patients who had LV aneurysm repair with an endocardial patch instead of those who had a standard linear repair [28, 41]. A clear technical trend from plication or excision to repair

incorporating an endoventricular technique with preservation and bypass to the LAD has occurred.

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Selection of Cardiac Valvular Prostheses

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Clinical Studies Reporting Long-Term Performance Results of Specific Prostheses

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The acquisition of new knowledge in thoracic surgery is a continuum. Ideas and practices may change significantly as a result of experience, but there have been limited ways to communicate easily the reasons for such modifications.

The purpose of this section is to present brief follow-up reports from authors whose work was previously published in *The Annals of Thoracic Surgery*. The goal is to learn whether the

original conclusions have stood the test of time, and whether or not previously recommended techniques have been modified, replaced, or discarded. Contributions to Update are short progress reports that do not preclude subsequent, more complete articles.

Thomas B. Ferguson, MD, Editor

John R. Benfield, MD, Associate Editor

1992: Effect of Internal Mammary Artery Dissection on Sternal Vascularization

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Internal mammary artery (IMA) dissection may cause sternal devascularization and ischemia resulting in sternal wound complication. To evaluate the effect of median sternotomy and IMA dissection on sternal vascular supply, sternal bone tomography was performed 7 days and 1 month after cardiac operation in 67 patients. Seventeen nondiabetic patients had single IMA grafts, 18 had double IMA grafts, and 12 had only saphenous vein grafts or valve replacement. Twenty diabetic patients were studied after any one of these operations. Seven patients were restudied 1 month after the operation. Sternal technetium-99m-methylene diphosphate tomography was performed. The sternum was visualized and focal zones of hypoactivity represented sternal hypoperfusion. The ratio of hypoactivity area over total sternal area was calculated for every patient. After median sternotomy without single or double IMA grafts, the

averaged hypoperfusion ratio was $4\% \pm 1\%$ compared with $13\% \pm 3\%$ after single IMA grafts and $24\% \pm 6\%$ after double IMA grafts ($p < 0.0001$). Diabetic patients without IMA, with single IMA, and with double IMAs showed hypoperfusion areas of $5\% \pm 3\%$, $15\% \pm 5\%$, and $23\% \pm 9\%$, respectively, a result similar to that of nondiabetic patients. One month after operation the hypoperfusion area decreased to $2\% \pm 2\%$ ($p < 0.05$) in restudied patients. Our results indicate that IMA dissection causes a significant although partial and temporary sternal ischemia, which is more severe after double IMA than single IMA mobilization and which may be incriminated in the development of sternal wound infection. This vascularization defect was not greater among patients with diabetes mellitus.

(*Ann Thorac Surg* 1992;53:115-9)

1993 Update: Michel Carrier, MD, Jean Grégoire, MD, Raymond Cartier, MD, Yves Leclerc, MD, and L. Conrad Pelletier, MD

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In a previous report [1], bilateral dissection of internal mammary arteries had been shown to cause partial and temporary devascularization of the sternum in the immediate postoperative period. This sternal ischemia could play a role in the increased incidence of wound complications when both mammary arteries are used for coronary artery bypass grafting. Recently, the inferior epigastric artery has been suggested in coronary artery bypass grafting as an alternative to saphenous vein grafts. In the experience reported by many authors, the inferior epigastric artery graft was associated with bilateral mammary artery grafts to obtain complete myocardial revascularization. Despite early clinical success, Barner and associates [2] described sternal and abdominal wound

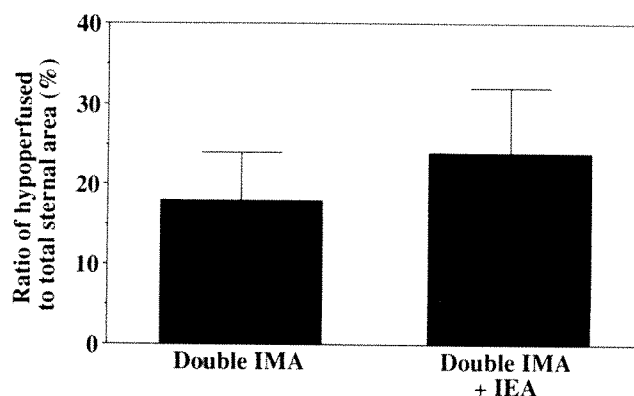


Fig 1. Ratio of hypoperfused to total sternal area 7 days after operation (mean $\pm$ standard error of the mean). There is no difference between groups. (IEA = inferior epigastric artery; IMA = internal mammary artery.)

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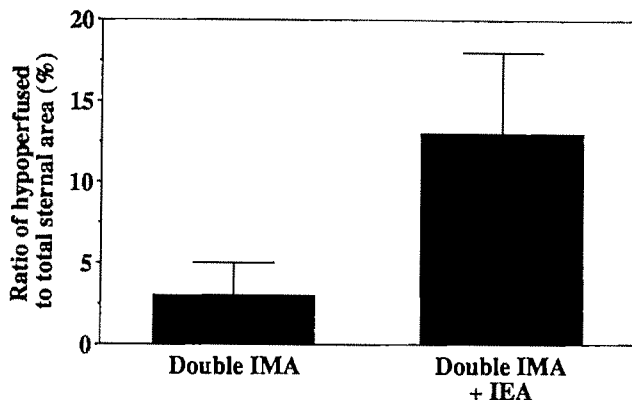


Fig 2. Ratio of hypoperfused to total sternal area 1 month after operation (mean $\pm$ standard error of the mean). There is a significant ($p < 0.05$) difference between groups. (IEA = inferior epigastric artery; IMA = internal mammary artery.)

complications in 2 patients who underwent inferior epigastric artery grafting.

Because the epigastric arteries are a source of collateral blood flow to the ischemic sternum after bilateral dissection of internal mammary arteries, the dissection and harvesting of epigastric arteries might increase sternal ischemia and the risk of wound complication after operation. The objective of this follow-up report is to evaluate the effect of dissection of bilateral mammary and epigastric arteries on sternal vascularization and wound healing.

Sternal bone tomography was performed 7 days and 1 month after bilateral mammary artery grafting with or without unilateral epigastric artery grafting in 22 patients. Sternal technetium 99m-methylene diphosphate tomography was performed. The total sternal area was delineated, and focal zones of hypoactivity representing sternal hypoperfusion were identified. In each patient, the ratio of the number of pixels in hypoactive areas to total sternal area was calculated.

Thirteen patients with bilateral internal mammary artery grafts were compared with 9 patients with bilateral mammary grafting associated with unilateral inferior epi-

gastric artery graft. Patient age and preoperative clinical and angiographic characteristics were similar in both groups. Seven days after operation, the average sternal hypoperfusion ratio was $18\% \pm 6\%$ after bilateral mammary artery grafting compared with $24\% \pm 8\%$ after epigastric and bilateral mammary grafting, a nonsignificant difference (Fig 1). One month after operation, the average hypoperfusion ratio in patients who underwent bilateral mammary artery grafting averaged $3\% \pm 2\%$ compared with $13\% \pm 5\%$ after epigastric and bilateral mammary artery dissection, a significant difference (Fig 2). No sternal wound complication was observed in either group of patients.

Our results indicate that unilateral epigastric with bilateral mammary artery dissection causes significant although partial and temporary sternal ischemia. Although not more severe, the hypoperfusion lasts longer when the epigastric artery mobilization is added to bilateral internal mammary artery harvesting. Adding epigastric artery dissection to bilateral mammary artery grafts could therefore increase the ischemic effect and the resulting risk of wound complication. Although the use of the inferior epigastric artery is gaining in popularity [3, 4], the indications are not yet well-defined. Our results suggest that bilateral mammary and epigastric artery grafting should probably be avoided when other risk factors for wound complication such as diabetes mellitus, chronic obstructive pulmonary disease, obesity, and advanced age are present.

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Thoracic Surgery Directors Association: 1992 in Review

Nineteen ninety-two was a year of increased activity and rejuvenation for the Thoracic Surgery Director's Association (TSDA). The Executive Committee—Drs Martin F. McKneally, President, Gordon F. Murray, President-Elect, Mark B. Orringer, Secretary-Treasurer, and Sidney Levitsky and Stanton P. Nolan, Executive Committee—began to refocus the Association on current issues important to our mission as educators and advocates of our residents. With the stimulus provided by the American Association for Thoracic Surgery (AATS) Retreat held at Snowbird, Utah, in September 1991, the TSDA continued the introspective evaluation now underway in our specialty, particularly in regard to resident education.

At the February 1, 1992, TSDA meeting in Orlando, Florida, the Association heard reports that paralleled the major topics discussed at the AATS Snowbird Retreat: Drs John Waldhausen on Cardiothoracic Resident Education; Andrew Wechsler on Cardiothoracic Research; Frank Spencer on the Cardiothoracic Surgeon and Social Responsibility; William Gay on Funding of Cardiothoracic Research; and George Magovern on the Scope of Cardiothoracic Surgery.

After a discussion of these presentations, a decision was made to plan a symposium on Alternative Approaches to Thoracic Surgical Education at the next TSDA meeting. Further, the idea was born that the TSDA and the Association of Program Directors in Surgery might begin to establish a dialogue to further discussions about the length and content of the thoracic surgery residency education curriculum. Doctor Ben Wilcox, Chairman of The Society of Thoracic Surgeons Ad Hoc Committee for Graduate Education, announced plans for a consensus conference on thoracic surgery residency education for Fall 1992. In an effort to provide a more fair and organized selection process for general surgery residents applying to thoracic surgery residency programs, a National Thoracic Surgery Resident Matching Program, endorsed by the TSDA Executive Committee, the American Board of Thoracic Surgery (ABTS), and the Residency Review Committee for Thoracic Surgery was enforced, and 84 of the 90 eligible residency programs (93%) were registered for the Match at the time of the February 1 meeting. In response to the proliferation of industry-supported courses being offered to thoracic surgery residents without specific documentation of their educational value, a Committee on Extramural Educational Programs chaired by Dr Stanton Nolan was appointed to develop a process for defining TSDA-approved resident education programs and the appropriate process for funding such programs in accord with the guidelines published on December 3, 1990, by the counsel on Ethical and Judicial Affairs of the American Medical Association regarding gifts to physicians from industry.

At the two TSDA meetings held in Los Angeles, California (April 25 and April 27, 1992), several important issues were discussed:

1. A successful Match for thoracic surgery resident selection for 1994 was completed in April 1992, with 93% of eligible programs participating. Of the 132 available residency positions in these programs, 123 (93%) were filled through the Match. Of the 183 residency applicants who participated in the Match, 123 (67%) matched; there were 60 (33%) unmatched applicants who applied for thoracic surgery residencies. Participation in the Match is now a condition for membership in the TSDA.
2. Doctor Ben Wilcox, Chairman of the ABTS, announced that at the April 1992 meeting, the Board voted to change its membership representation to include two representatives from the TSDA. This change is viewed as a substantial step in strengthening the efforts of both the ABTS and the TSDA.
3. Because of the October 1989 decision of the ABTS to no longer accept for the certifying examination candidates trained in Canadian programs (effective for residents beginning their training July 1, 1992), the TSDA Executive Committee recommended a Bylaws change that would give Canadian Program Directors Associate Member status (rather than severing ties with the Canadian Program Directors). Discussion of this recommendation is ongoing.

A symposium on Alternative Approaches to Thoracic Surgery Residency Education was held at the April 25, 1992, meeting and included the following five presentations:

1. "Is certification in general surgery essential for the practice of cardiothoracic surgery in the 1990s?"—Randall Griepp.
2. "The ideal general surgery curriculum for entry into thoracic surgery residencies—the blended program"—Sidney Levitsky.
3. "The case for the traditional two-year thoracic surgery residency"—Mark Orringer.
4. "The integrated Hopkins model"—Bruce Reitz.
5. "The current structure of general surgery—bearing the gold standard"—Gordon Murray.

After discussion of these presentations, there was a general consensus about the need to better define the components of the curriculum both in General Surgery and Thoracic Surgery residency education. The TSDA looks forward to receiving the report of the Joint Conference on Graduate Education in Thoracic Surgery held in

Oak Brook, Illinois, in September 1992. That report will be the focus of the next TSDA meeting in January 1993.

On October 10, 1992, in New Orleans, during the meeting of the American College of Surgeons, the TSDA Executive Committee met informally with officers of the Association of Program Directors in Surgery and the Chairmen of their respective Residency Review Committees to initiate a dialogue about improving the curriculum for residents planning careers in thoracic surgery. The ultimate goal of these and future such meetings is to ensure that the specialty of thoracic surgery is involved

early in the teaching of our future trainees and that it exerts a steering effort on their programs while they are in general surgery residency. The task before us is to define the important components of the thoracic surgery curriculum so that we can have a starting point for negotiations with our general surgery counterparts. This will be the mandate of the TSDA Committee on Curriculum and Education chaired by Dr Andrew Wechsler.

Mark B. Orringer, MD
Secretary/Treasurer

REVIEW OF RECENT BOOKS

Near Misses in Cardiac Surgery

By Myles Edwin Lee, MD

Stoneham, MA, Butterworth Heinemann, 1992

146 pp, \$29.95

Reviewed by John H. Calhoon, MD

Doctor Lee has collected a summary of some 40 cases encountered during his practice. Easily readable completely in two to three hours, this text reviews a number of sand traps in the fairways of thoracic surgery. Doctor Lee had the misfortune of finding these traps and subsequently extricating himself with a minimum of penalty. Covered in these vignettes are how to deal with difficult redo procedures, the ill-prepared surgical patient,

the misinformed medical colleague, cardiopulmonary bypass disasters, and a variety of looks at aortic dissections. As I gleaned these pages, I couldn't help but feel that his case studies would be enlightening to the surgical resident, the young cardiac surgeon preparing for a board examination, or the most seasoned of thoracic surgery practitioners. Although a number of the cases may be a review of bad experiences for most, it was my strong feeling that there is something in this book for everyone. His discussions of each problem were brief, yet sage and complete. I found the book highly enjoyable. I think it is appropriate reading for all who practice cardiovascular surgery.

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Venting and Deairing Without a Roller Pump

To the Editor:

It was refreshing to read the article on simple and safe technique for left ventricular venting by Lundy and associates [1]. "Standard" techniques that suck away blood and air using roller pumps under varying levels of negative pressure from varying locations are accepted without critical evaluation. These should result in cellular trauma and carry added risk of infection due to admixture with room air.

We have adopted the following venting and deairing procedure, with a desire to make it as gentle as venous return and avoid expenses due to a vent suction line incorporating a pump [2, 3]. A cannula is inserted into the left atrium and connected to the venous return line. Before cardiotomy the blood in the lesser circulation is drained into the pump. During bypass in patients whose mitral valve is competent and interatrial septum is intact, such as in tetralogy of Fallot, ventricular septal defect, and left ventricular outflow obstruction, the vent is kept open and keeps the field dry, minimizing the need for cardiotomy suction. In others, the vent is temporarily clamped. After repair is completed the vent is reopened and drains initially air and blood and later only blood into the venous line. The left ventricle is gently squeezed after making the mitral valve incompetent by distorting it by external pressure.

In patients with grossly dilated left ventricle or in whom aortic leak is anticipated, the vent is advanced into the left ventricle to keep it unloaded as long as necessary in addition to serving as an air vent. In patients undergoing redo open mitral valvotomy, we believe it is unnecessary to free the adhesions and release the left ventricle [4]. To deair and decompress the left ventricle, we advance the vent into the apex of the left ventricle, which is tethered anteriorly. A malleable wire inside the vent catheter helps to mold the catheter into a suitable curve and retains it in situ [3].

In patients whose left heart is not opened (bypass operations) the vent is inserted into the main pulmonary artery and connected to the venous return. We have found hardly any need to suck blood away from the coronary arteriotomy.

This method has the following advantages. There is "gentle" venting and deairing and less trauma. It is economical because a vent pump circuit is not necessary. It can be maintained as long as necessary, and keeps the left ventricle unloaded.

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Measurement of Instantaneous Pulmonary Capillary Blood Flow

To the Editor:

In 1971, *The Annals* published the work of Greenberg and associates [1], in which instantaneous pulmonary capillary blood flow was measured with the nitrous oxide (N_2O) method using a pneumotachograph (nonplethysmographic method or airway volume change method) in surgical patients. Their work was also quoted in the *Handbook of Physiology* [2] in 1987. I believe the method they used in that study deserves some comment.

If an N_2O body plethysmographic method is used for the measurement of pulmonary capillary blood flow, the box flow meter should show inward gas flow into the box as the pressure in the box decreases due to N_2O absorption [2]. Likewise, Greenberg and associates [1] assumed that if an N_2O -pneumotachographic method is used, there will be inward gas flow into the airway as alveolar gas pressure decreases due to N_2O absorption by pulmonary capillary blood. Accordingly, the gas flow tracing during breath holding on air was subtracted from that after N_2O inhalation to derive the capillary flow.

I used an N_2O -pneumotachographic method to obtain the pulmonary capillary blood flow, from which pulmonary artery systolic storage volume fraction could be measured in anesthetized patients. The pneumotachograph was connected to the airway (endotracheal tube) in such a way that the outward gas flow produced positive or upward waves. Surprisingly, there was no inward gas flow into the airway during apnea on air or after N_2O inhalation. Instead, there was an outward pulsatile gas flow during apnea both on air and after N_2O inhalation, and the gas flow after N_2O inhalation was lower than that on air, suggesting that the gas flow after N_2O inhalation was attenuated due to N_2O uptake by pulmonary capillary blood flow as shown in Figures 1 and 2. In Figure 2, to obtain a whole cycle of pulmonary capillary blood flow wave, the gas flow tracings

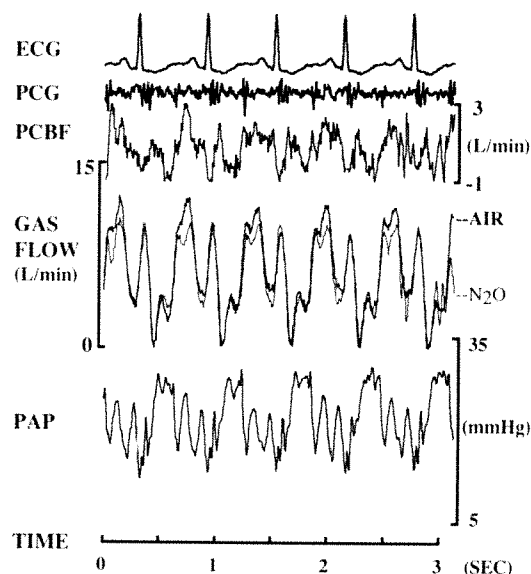


Fig 1. Pneumotachograph gas flow recordings in an anesthetized patient. The gas flow tracing after N_2O inhalation was superimposed over that on air during apnea. (This study was approved by the Institutional Review Board.) (ECG = electrocardiogram; PAP = pulmonary artery pressure; PCBF = pulmonary capillary blood flow; PCG = phonocardiogram.)

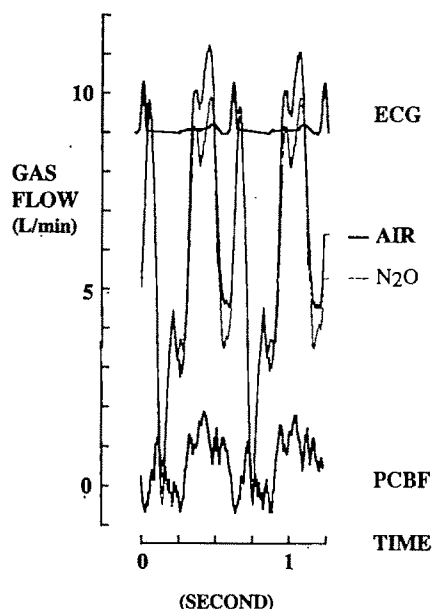


Fig 2. A whole cycle of pulmonary capillary blood flow wave tracing (not smoothed). (ECG = electrocardiogram; PCBF = pulmonary capillary blood flow.)

within the interval of two R waves of the electrocardiogram were averaged, and the gas flow tracing after N_2O administration was subtracted from that on air.

My observation is consistent with the findings of the previous study by Wasserman and Comroe [3]. The gas flow (Krogh spirometer volume) tracing after inhalation of N_2O was smaller than that after inhalation of air, and subtracted from the tracing after inhalation of air to derive pulmonary capillary blood flow.

It is not clear why the pattern of the gas flow in the study by Greenberg and associates [1] is different from that in my study or others'. Because the pulsatile gas flow during apnea is produced by the pulmonary capillary pulsation, the gas flow during apnea both on air and after N_2O inhalation should be an outward flow. Thus, one cannot subtract the gas flow tracing on air from that after N_2O inhalation, because the gas flow tracing after N_2O inhalation is smaller than that on air. Reexamination of this point is warranted.

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Surgical Management of Spontaneous Pneumothorax in Patients With AIDS

To the Editor:

Doctor Fleisher and associates [1] have published an excellent article on surgical treatment of spontaneous pneumothorax in patients with acquired immunodeficiency syndrome (AIDS). Recently, we had occasion to treat an AIDS patient with recurrent bilateral pneumothorax, as a consequence of aerosolized pentamidine prophylaxis, which required surgical treatment to resolve.

In the last 2 years the administration of aerosolized pentamidine in patients infected with human immunodeficiency virus (HIV) has become general practice as a prophylaxis against *Pneumocystis carinii* pneumonia [2]. At the same time there have been more and more reports of atypical relapses of upper-lobe *P. carinii* pneumonia with the development of parenchymatous cavitation, bronchopleural fistula, and subsequent pneumothorax [3], no doubt due to the poorer distribution of the drug in the lung apices and in the peripheral areas [4]. In fact, it is accepted that if pneumothorax develops in one of these patients, this opportunistic infection should be suspected [5].

Our patient initially required thoracic drainage, but because of persistent air leakage through the drainage system surgical treatment was indicated. A right axillary thoracotomy was carried out, with resection of the apical bullous complex. Forty-eight hours after operation the patient exhibited contralateral pneumothorax, which was treated by drainage but also required operation due to persistent leakage. After 6 months, the patient remains asymptomatic.

For these patients, we recommend thoracic drainage using a water-sealed closed system, with or without aspiration, as an initial treatment. When air leakage persists for more than 8 days surgical treatment is indicated. In cases of bilateral pneumothorax, when operation is indicated we believe—along with other authors [1, 6]—that median sternotomy is the access route of choice.

This case illustrates that although aerosolized pentamidine is effective as a prophylaxis against *P. carinii* pneumonia, it is not free from untoward side effects. Because of the effects described, we believe that in the future the administration of pentamidine with the patient in a supine position should be considered, and the efficacy of other drugs such as cotrimoxazole, dapsone, or pyrimethamine for these patients should be appraised. Also, we should acknowledge the contribution of videothoracoscopy, a technique used in our service in 5 patients with pneumothorax (1 of whom was HIV-positive) since January 1992, with completely satisfactory results.

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Reply

To the Editor:

We read with interest Dr Albort and colleagues' letter regarding the surgical management of bilateral spontaneous pneumothoraces in a patient with AIDS. Because a left spontaneous pneumothorax developed in their patient after a right thoracotomy for treatment of a right spontaneous pneumothorax, they recommend a median sternotomy as the incision of choice for the management of these patients.

We reported our initial experience of spontaneous pneumothorax in AIDS patients in 1988 [1]. One patient required a left thoracotomy with stapling of cysts and an apical pleurectomy for a recurrent pneumothorax with a persistent air leak. In addition, this patient had a small right apical synchronous pneumothorax noted on chest roentgenogram, which was treated with closed tube thoracostomy. He was discharged, but readmitted shortly after with a large right pneumothorax, which eventually required a right thoracotomy. At the time, we questioned whether patients requiring operation for synchronous pneumothoraces would be best treated with a median sternotomy and a single bilateral procedure.

The recent advent of video-assisted thoracic surgery has changed our opinion on the possible use of a median sternotomy. We now recommend video-assisted stapled resection of the cystic disease with an apical pleurectomy or pleural abrasion for the treatment of spontaneous pneumothorax in AIDS patients.

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Heparin-Induced Thrombocytopenia

To the Editor:

We were quite interested in reading the article by Dr Walls and associates entitled "Heparin-induced thrombocytopenia in open heart surgical patients: sequelae of late recognition" [1]. They reviewed retrospectively patients with heparin-dependent antibodies. Those diagnosed preoperatively did not receive any

further heparin after reversal with protamine sulfate and did not suffer any complications. The group recognized postoperatively had a high incidence of bleeding (53%) and thromboembolic events (44%).

We recently had a similar patient who was known preoperatively to have a heparin allergy diagnosed after a thromboembolic event. Thus the precaution of no further heparin after reversal with protamine was taken. Unfortunately, because of hemodynamic instability, he required an intraaortic balloon pump. Peripheral artery thrombosis and renal failure developed, and the patient died soon after of dysrhythmia from which he could not be resuscitated.

This case illustrates that, unfortunately, knowing beforehand of the presence of a heparin allergy and taking the usual precautions does not prevent the occurrence of thromboembolic complications, especially in the presence of an intraaortic balloon pump.

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Lung Cancer in the Young

To the Editor:

We read with interest the report in your journal by Icard and associates [1] and were impressed by the unusually large population of young lung cancer patients. Their data led logically to the conclusion that in young patients with a stage of lung cancer for which surgery is an option, the disease process appears to behave as it does in an older population. However, we cannot accept their implication that lung cancer in young people is not an aggressive form of the disease.

In response to their report, we reviewed our experience at a tertiary care referral center in the United States. We retrieved computerized tumor registry files from the past 15 years (1977 to 1992) and identified 23 patients with bronchogenic carcinoma who were less than 40 years old. Medical records were reviewed for comparison with the parameters evaluated in Icard and associates' report.

Many of our observations agree with those of Icard and associates and with previously published studies [2-4] (Table 1). The male to female ratio, duration of symptoms before presentation, percentage of smokers, and percentage of histologic diagnoses are similar. However, the series reported by Icard and associates is highly selected because patients are referred to their center for operations, and inoperable cases are not admitted. By excluding all patients with stage IV disease, Icard and associates ignore a very important behavior characteristic of lung cancer in young people. Late-stage presentation and therefore inoperability is very common in the young age group, much more common than in the general population. In our series, fully 86% of patients were staged IIb or IV at presentation. This contrasts dramatically with published data on the general population, where late-stage

Table 1. Studies of Primary Lung Cancer in Patients Less Than 40 Years of Age

Variable	Pemberton et al [2]	DeCaro and Benfield [3]	Antkowiak et al [4]	WRAMC	Icard et al [1]
Years encompassed	1956-1979	1959-1979	1973-1989	1977-1992	1982-1990
No. of patients	112	35	89	23	82
Male to female ratio	3.3	1.5	1.6	3.6	7.2
% Symptomatic	92	97	96	90	66
Duration of symptoms (mo)	4.2	3.2	2.4	2.6	4.0
% Smokers	87	97	88	80	89
% Adenocarcinoma	32	49	80	43	42
% Squamous cell	27	17	7	17	28
% Small cell	21	28	10	4.3	8.5
% Large cell	20	2.8	30	13	6.0
% NSCC or mixed	...	...	...	21	10
% Stage I	7.9	...	2.0	9.5	26
% Stage II	5.3	...	3.0	4.8	12
% Stage III	86	...	66	53	61
% Stage IV	...	...	29	33	...

NSCC = non-small cell carcinoma; WRAMC = Walter Reed Army Medical Center.

presentation (IIb and IV) is markedly less common, approximating 40% of all cases [5].

Icard and colleagues conclude that for young people, "primary lung cancer seems to be related more to the extent of the disease than to a particularly aggressive behavior pattern of the cancer." Although this conclusion is supported superficially by their data, it does not explain the larger question of why cancers in young people so often present in late, inoperable stages.

Although it is possible that young adults present with advanced disease because they remain asymptomatic or ignore symptoms longer, published statistics demonstrate that more than 90% of young lung cancer patients have symptoms at time of presentation [2-4], no different from older people, and that the duration of symptoms at presentation ranges from 2 to 4 months. In older age groups, duration of symptoms before presentation is reported to be at least 4 months [6, 7] and longer even for alarming symptoms such as hemoptysis [8].

Perhaps the favorable experience reported by Icard and colleagues is a result of an unusual referral process or differences in access to medical care compared with other populations studied. This hypothesis is supported by a major difference their report has with the other series, namely, the lower number of symptomatic patients at time of presentation (66% versus 90%).

We concur with the reasoning applied to the data presented by Icard and associates, but we cannot accept their final conclusion. Their work adds important new information to our understanding of the value of an aggressive surgical approach to lung cancer in young people. However, their favorable experience is not shared by their internal medicine colleagues. The fact that most lung cancers in young people present in late, inoperable stages of the disease argues for an aggressive behavior pattern of the cancer.

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Reply

To the Editor:

We agree with Drs McCambridge and Eliasson that our population represents a highly selected series because these patients were referred to our center for operations. Our purpose was not to determine the overall prognosis of lung cancer in young patients, which is not possible for a surgical team, but to demonstrate that patients less than 40 years old with resected lung cancer will have a prognosis similar to that of older patients at an equal TNM stage. These results justify our aggressive surgical policy for young patients.

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Cervical Esophageal Anastomosis

To the Editor:

I greatly appreciated the interest of Charles D. Fraser and associates [1] in reestablishing the continuity of the cervical

esophagus by a limited local procedure, after a Johnson-type exclusion having a proximal end esophagostomy. I agree with them that whenever possible, a total esophageal substitution should be avoided in these unfavorable conditions created by the previous esophageal perforation. But I disagree with the concept that for a total esophageal exclusion and diversion, the classic esophageal transection is the only currently available technical modality.

A fundamentally new procedure was introduced by Urschel and associates [2] in 1974, using banding to occlude the esophagus below the perforation, combined with side cervical esophagostomy, to avoid the need of a further esophageal replacement.

This type of exclusion was performed successfully (through a laparotomy) in a 9-day-old traumatic lesion [3] after the primary suture of this 15-cm-long tear, with side cervical esophagostomy; in another instance a 6-week-old iatrogenic disruption with right-sided empyema was treated with a similar distal and also cervical banding [4] with tube thoracostomy for suction-lavage. Neither stricture nor need for a late dilation was noted after the subsequent removal of the bands after 10 and 21 days, respectively.

I would like to call attention to the usefulness of this organ-preserving technique, performed simultaneously with the primary repair or after the failure of the initial attempt at esophageal closure. If previously an end-type proximal esophageal diversion has been done, undoubtedly a segmental reconstruction of the esophagus is more advantageous.

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Thoracoscopy and Spontaneous Pneumothorax

To the Editor:

With greatest attention we have read the interesting work of Drs Olsen and Andersen [1], and we would like to make the following commentaries.

Based on the high incidence of blebs and bullae in patients with relapsing spontaneous pneumothorax (SP) and on the statistical significance of these as cause of the relapse [2], we elaborated a scheme of treatment of SP that centers around the performance of a thoracoscopy in the first episode [3], like Olsen and Andersen. Thus, between July 1983 and December 1990 we have performed 366 thorascopies, 107 of which were performed in 104 patients with SP, 3 of whom had bilateral pneumothorax that was not simultaneous. Eighty-nine thorascopies were performed for primary or idiopathic SP, and 18 for secondary SP. Patient ages ranged between 15 and 72 years (mean age, 29.4 years); there were 89 men and 15 women.

We always performed the exploration with local anesthesia, and only in 4 cases was sedation added. The local anesthesia

permitted us to perform a Valsalva maneuver to visualize perforated or collapsed bullae or blebs. We classified the endoscopic findings into four types, modifying the classification of Vanderschueren [4]: type I = normal exploration (26 patients; 24%); type II = cicatricial complex apical, single bleb or bulla < 2 cm with or without adhesions (22 cases; 21%); type III = multiple adhesions (7 cases; 7%); and type IV = multiple blebs or bullae < 2 cm, bulla > 2 cm, dystrophie bullae, with or without adhesions (49 cases; 46%); there were 3 cases of lung fibrosis (3%). All these patients have been followed up for at least 18 months. As Olsen and Andersen reported, 80% of the relapses take place before the first year.

All patients with type I SP were treated with aspirative drainage as the only measure. Relapse occurred in 1 of 26 (3.8%); at intervention we found that a plain bulla had passed unnoticed. Of the type II patients 1 was at first operated on and the rest were treated with aspirative drainage. Relapse occurred in 1 of 21 (4.7%); at intervention we found that the bulla was not single but multiple. Of the type III patients 1 was operated on at first and the rest were treated with aspirative drainage. Relapse occurred in 5 of 6 (83.3%). Of the type IV patients, 28 were operated on at first and the rest were treated with aspirative drainage. Relapse occurred in 13 of 21 (62%). The difference in relapse rate between groups is highly significant ($p < 0.0001$).

We agree with Olsen and Andersen that thoracoscopy is an excellent method of selection to guide the treatment of the patients with SP, but we would like to go even further. Probably in all patients with types I and II SP, which is almost half (46%), it is not necessary to add pleurodesis, assuming the minimal relapse of SP shown by our experience. Nonetheless, we should direct all our attention to the patients with types III and IV, to whom we can apply a technique of thoracoscopic surgery assisted by video to realize liberation of adhesions and resection of bullae and blebs with endosuture or laser. We prefer to add mechanical pleurodesis instead of partial pleurectomy for the same reasons given by Olsen and Andersen.

In conclusion, we consider thoracoscopy a useful method of selection for patients with SP, directing them to simple thoracic drainage in types I and II or toward thoracoscopic surgery assisted by video or conventional surgery in types III and IV.

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Transplantation Using Donor Hearts From Patients With Circulatory Arrest

To the Editor:

The article by Gundry and associates [1] reported experimental experience in the resuscitation and transplantation of 4 lamb

hearts arrested for 30 minutes after exsanguination. Although the number of experiments is small, this is an interesting study that may eventually lead to an increased number of pediatric donor hearts for transplantation. Whether the same encouraging results could be obtained using adult rather than juvenile hearts remains uncertain.

Based on previous data in the literature, the posttransplantation period of functional assessment of these hearts (of only 30 minutes) may well be inadequate. Ecker and colleagues [2] showed that a 1-hour period of anoxic arrest of the dog heart depressed function immediately and markedly. Although there was a steady improvement in contractility during the initial 2 to 2½ hours after restoration of coronary flow, contractility remained impaired as compared with that of nonischemic hearts. This difference tended to widen in the 72 hours after the ischemic period in spite of complete metabolic and circulatory support.

My own observations in adult dogs, published almost 20 years ago [3-5], would suggest that the mode of death of the animal is a major factor in the potential success of resuscitation. In these experiments the chest was opened and the heart and lungs were isolated from the remainder of the circulation by ligation of the superior and inferior venae cavae and clamping of the aorta proximal to the branches to the head and neck. By isolating the heart and lungs from the rest of the body, acidosis occurring in damaged ischemic organs, such as the liver, no longer affected attempts to resuscitate the heart. The heart, resuscitated by manual massage and defibrillation, supported the coronary and pulmonary circulations only and was relieved of the burden of supporting the entire systemic circulation.

Consistent resuscitation of the *asphyxiated* heart could be obtained after anoxic intervals of up to approximately 30 minutes, but was generally unsuccessful after longer periods. Successful resuscitation was obtained more readily and after longer periods of arrest in the *exsanguinated* (50 minutes) or *electrically fibrillated* (90 minutes) heart. These findings correlated well with those of other studies and, in particular, with those of Lundsgaard-Hansen and associates [6], who, in 1971, found that asphyxia caused much more myocardial damage than exsanguination and that the mode of death was at least as important for the postmortem metabolic state of the heart as the warm ischemic time.

Visual observations made on hearts in animals being asphyxiated or exsanguinated threw considerable light on why asphyxia should be more damaging to the myocardium [5]. Hearts in dogs undergoing anoxic death were forced to attempt to support an entire circulatory workload while functioning in an increasingly hypoxic environment. As the myocardium failed, the chambers of the heart became grossly distended, almost certainly adding to the damage of the myocardium.

Under conditions of exsanguination, however, the blood was being well oxygenated throughout the agonal period. The heart, therefore, was obtaining an adequate oxygen supply until the animal became grossly hypovolemic. Throughout this period, the workload that the heart was being forced to maintain was steadily decreasing as exsanguination continued. By the time the myocardium was experiencing the effects of hypoxia, the circulatory workload was minimal. The heart was at no time put under the adverse conditions met with during death from asphyxia. This was reflected in the absence of distention of any of the chambers of the heart, and also in the fall in maximum time derivative of pressure to only 73% of the control level compared with a reduction to 36% in asphyxiated animals. After resuscitation, very rapid improvement in parameters of left ventricular contractility was recorded in the exsanguinated animals, in

contrast to the slower improvement observed in the asphyxiated group.

In the clinical situation it may be impossible to heparinize the donor's blood before circulatory arrest. There is evidence that circulatory arrest in the nonheparinized subject leads to intravascular clotting, which occludes the small vessels and capillary networks, and this has been shown to lead to greater difficulty in resuscitation of any organ. The experience of Gundry and his colleagues, who achieved good initial resuscitation after flushing the donor heart with a solution that contained streptokinase, is therefore particularly important. The majority of dogs in my own studies were heparinized before the induction of cardiac arrest, but resuscitation was attempted in 5 nonheparinized, asphyxiated hearts, with 3 hearts returning to good cardiac activity after anoxic periods of 20, 40, and 55 minutes, respectively [5].

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Reply

To the Editor:

My associates and I are indebted to the pioneering efforts of Doctor Cooper and his colleagues in their attempts to extend the supply of donors for human heart transplantation. As demonstrated in his letter, these efforts began more than 20 years ago, and his results parallel those observed in our experiments in which we successfully reanimated hearts from exsanguinated, dead donors. Doctor Cooper's cautionary notes regarding poor long-term organ function after resuscitation need to be further tested experimentally; however, our own clinical experience using hearts from infants receiving cardiopulmonary resuscitation for up to 1 hour reveal no early or late decrements in systolic or diastolic function, as studied up to 2 years after transplantation [1].

Although our article in *The Annals* only addressed the subject of exsanguinated animals, Dr Cooper also stresses the differences between exsanguinated animals and animals that died of anoxia, suggesting with experimental evidence that the latter makes a much more difficult model for successful resuscitation. We have recently repeated our experiments using an anoxic model of arrest, with a 30-minute waiting period beyond cardiac standstill

for harvest (40 ± 5 minutes after start of anoxia) and using retrograde coronary sinus reperfusion, and have again easily separated all animals from bypass after transplantation [2]. Therefore, we believe that the mode and methods of reperfusion, rather than the mechanisms of death, are the most important factors predicting resuscitation success.

Despite these encouraging findings, it is essential that investigators focus further efforts into defining the ultimate period of warm ischemia that hearts of different ages from various species can sustain and still be successfully reanimated, and whether such hearts will function long-term.

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Beneficial Effect of Nicardipine on Perioperative Myocardial Ischemia

To the Editor:

In spite of a dramatic improvement in myocardial preservation techniques, cell damage may still occur during cardiopulmonary bypass (CPB). This can be expressed as postoperative increase in creatinine kinase or as early perioperative electrocardiographically identifiable ischemia. This may be observed in any kind of operation using CPB, although the additional contribution of coronary artery disease and coronary artery bypass grafting operation renders it more problematic. Duration of CPB, graft occlusion, inadequate flow through an internal mammary artery

graft, and ventricular hypertrophy have been shown to enhance the risk of perioperative myocardial ischemia. Whatever the cause, perioperative myocardial ischemia can lead to permanent ventricular dysfunction if not promptly resolved. In the absence of anatomical or technical abnormalities that could be perioperatively corrected, coronary artery spasm and low-reflow phenomenon would be the most probable causes of perioperative myocardial ischemia.

Specific pharmacological treatment could play a crucial role. Nicardipine, a calcium-channel blocker, would appear to be the drug of choice in such a circumstance because of its specific coronary dilating property, its minimal negative inotropic effect (when compared with nifedipine), its potent systemic vasodilatory action, and its inhibitory effect on endothelin secretion. One of us has previously reported the beneficial effect of intracoronary infusion of a large dose of nifedipine in patients suspected of having coronary spasm in the postoperative course of coronary artery bypass grafting [1, 2]. However, the above-mentioned properties of nicardipine and their possible synergetic effect prompted us to use this drug in similar circumstances of perioperative myocardial ischemia when other means were shown to be unsuccessful.

Between February and December 1991, 12 patients with perioperative myocardial ischemia have been successfully treated by intracoronary infusion of nicardipine in our institution. In all cases myocardial preservation has been achieved by the combination of antegrade and retrograde crystalloid cardioplegia (St. Thomas No. 1), topical cooling, and moderate systemic hypothermia (30°C). Patients' characteristics, the onset and degree of ischemia, dose and route of administration of nicardipine, and electrocardiographical evolution are reported in Table 1. The 11 patients who underwent coronary artery bypass grafting showed ST segment elevation in at least one revascularized area. In the patient who received a heart transplant the anterior part of the heart was involved. Six patients displayed severe hemodynamic alteration. The onset of perioperative myocardial ischemia ranged from 1 to 13 minutes after weaning off CPB. The grafts were explored and shown to be patent and nontwisted. Although all the patients were put back on CPB at least once and received nitrates and inotropes, no electrocardiographical improvement was observed. However, ST segment was normalized within a period ranging from 1 to 7 minutes after administration of a 5-mg bolus of nicardipine. Nicardipine administration was usually

Table 1. Nicardipine in Perioperative Myocardial Ischemia

Patient No.	Age (y)	Sex	Procedure	Time of CPB (min)	Onset (min after CPB)	ST segment elevation (mm)	Route	Dose (mg)	Onset of ST normalization (min after NIC infusion)
1	25	F	Heart Tx	130	5	3.0 anterior	AR	5	6
2	64	M	CABG 2 IMA	40	3	2.7 anterior	AR	4	5
3	68	F	CABG 2 SG	45	7	2.0 anterior	SG	5	3
4	76	F	CABG 3 SG	66	4	3.0 anterior	AR	2	2
5	64	M	CABG IMA	35	5	2.9 anterior	AR	5	1
6	76	M	CABG 4 SG	75	3	2.5 inferior	SG	5	3
7	75	M	CABG IMA, 2 SG	69	6	2.0 anterior	AR	5	3
8	71	M	CABG IMA, 1 SG	55	1	1.5 anterior	AR	5	2
9	56	M	CABG 2 IMA	56	13	2.8 anterior	AR	5	7
10	66	M	CABG IMA, GEA	78	4	1.9 inferior	AR	5	3
11	66	M	CABG IMA, 2 SG	75	10	2.5 anterior	AR	5	6
12	61	M	CABG IMA, GEA	67	7	3.0 anterior	AR	5	4

AR = aortic root; CABG = coronary artery bypass grafting; GEA = gastroepiploic artery; IMA = internal mammary artery; NIC = nicardipine; SG = saphenous vein graft; Tx = transplantation.

followed by a short period of deep systemic hypotension and electromechanical cardiac arrest. It is therefore mandatory to administer such a dose of nicardipine during full-flow CPB. When electrocardiographic changes were only observed in a territory revascularized by a vein graft, this was used as a unique route of injection (patients 3 and 6). All patients were subsequently weaned off CPB and had an uneventful postoperative course. No evidence of myocardial infarction has been shown in any of them.

Experimental and clinical data have clearly shown the protective effect of parenteral administration of nicardipine on various forms of myocardial ischemia [3, 4], eg, limitation of myocardial infarction size after coronary artery ligation, prevention and delay of the transient ischemia occurring during percutaneous transluminal coronary angioplasty, and improvement of perfusion in areas chronically ischemic. Our preliminary data strongly suggest that intracoronary bolus infusion of nicardipine could dramatically modify the outcome of perioperative myocardial ischemia after CPB.

This beneficial effect of nicardipine could be explained on several grounds. The inhibition of myocardial adenosine triphosphate breakdown might be crucial immediately after cardioplegic arrest, as the myocardium is restoring energy. The coronary dilating selectivity [4] leads to the enhancement of collateral blood flow, and this could have a beneficial effect on coronary artery spasm. In that respect, although the mechanism of coronary spasm is not known, calcium ions are thought to play a key role in the genesis of spasm [5]. As a calcium-channel blocker with an inhibitory effect on endothelin, nicardipine might counteract the spasm via those two pathways. The low-reflow phenomenon, an impairment of postischemic coronary flow, is an important issue to be addressed. Indeed, one of us has recently provided experimental data indicating clearly that low reflow can be enhanced by coronary dilating drugs with a subsequent improvement of postischemic recovery of cardiac mechanical function after prolonged cardioplegic arrest [6].

In conclusion, we believe that in the presence of perioperative myocardial ischemia without any anatomical cause, nicardipine can be used as the drug of choice as a last resort. We believe that the pharmacological properties of nicardipine could explain an improvement of low reflow and coronary spasm, the most probable causes of perioperative myocardial ischemia when anatomical etiology has been ruled out.

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Open Lung Biopsy

To the Editor:

I would like to congratulate Drs Chechani, Landreneau, and Shaikh [1] for finally refuting the last conclusion of Gaensler and Carrington's previously considered landmark article on open lung biopsy. Despite multiple inaccuracies, unfortunately, that study has been considered the "gold standard" for managing patients with diffuse pulmonary disease refractory to medical management [2]. This, misinformation, however, has hampered chest physicians for approximately 30 years.

Doctors Gaensler and Carrington declared that biopsy of the roentgenographically most involved region (usually the lower lobes) in patients with chronic diffuse interstitial lung disease is likely to show meaningless histological findings and that biopsy of lingular and middle lobes should be avoided [2, 3]. These inappropriate conclusions were initially refuted when I reported the results of my study demonstrating the significant sensitivity and specificity of lingular biopsies in patients with similar pathology [4, 5].

Doctor Miller and associates [6] subsequently confirmed our results and then refuted Drs Gaensler and Carrington's conclusions concerning right middle lobe biopsies. Dr Chechani and associates [1] have proven that biopsies of the roentgenographically most involved region are similarly most significant histologically, finally disproving Gaensler and Carrington's last conclusion.

It is imperative that the misinformation espoused by Drs Gaensler and Carrington finally be laid to rest to aid in the resolution of the management of a vexing and extremely important clinical problem. This entity is of added importance to thoracic surgeons, as many patients with diffuse interstitial lung disease are hemodynamically compromised and extremely ill. A surgical approach that is simpler and expeditious while offering a definitive diagnosis is thusly extremely advantageous [4, 5]. With the increasing use of thoracoscopy, biopsy of the lingula or right middle lobe may be somewhat less important but still should be remembered as an approach that satisfies the above criteria for bilateral diffuse pulmonary disease, and is another alternative in the armamentarium of the thoracic surgeon.

Lewis Wetstein, MD

143 South St
Freehold, NJ 07728

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Southern Thoracic Surgical Association

Rules for Submission of Abstracts

Abstracts for papers to be presented for the 1993 Annual Meeting are now being accepted. The deadline for postmark of abstracts is May 15, 1993. An original and one copy should be submitted, using the official Association abstract form, to Harvey I. Pass, MD, Chairman, Program Committee, the Southern Thoracic Surgical Association, 401 North Michigan Avenue, Chicago, IL 60611-4267. Additional forms are available upon request from the Association.

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Please send a CV and letters of recommendation to George J. Magovern, MD, Professor and Chairman of Surgery, Allegheny General Hospital and the Allegheny Campus of the Medical College of Pennsylvania, 320 E North Ave, Pittsburgh, PA 15212. 827A/D

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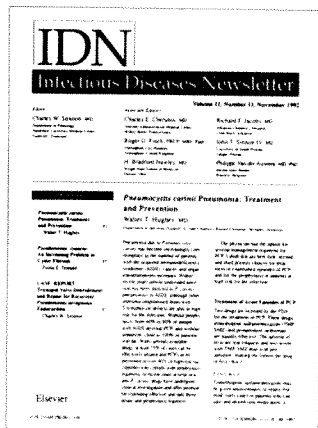
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The Lankenau Hospital and Medical Research Center is a state-of-the-art medical teaching and research facility nestled in a beautiful, yet convenient suburban Philadelphia location. This past year we performed over 800 open heart surgeries including surgery for atrial and ventricular arrhythmias.

We will have a position available July 1, 1993 on our staff for a Cardiothoracic Surgical Fellow. The ideal candidate should be board eligible or certified in general surgery. Board eligible in thoracic surgery highly desired. A Pennsylvania license is a must. Clinical Fellows are welcome to apply.

Along with top of the line technology and professional colleagues, the position offers medical benefits, no city wage tax deducted and a non-smoking environment. For further information, please forward CV to: Dr. Scott M. Goldman, Chief, Division of Thoracic & Cardiovascular Surgery, c/o Personnel Department, 100 Lancaster Avenue, west of City Line, Wynnwood, PA 19096.



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Cardiothoracic Surgeon

The Department of Surgery at the Dartmouth-Hitchcock Medical Center in Lebanon, New Hampshire is searching for an additional academic Cardiothoracic Surgeon at the Assistant/Associate Professor level. Candidates for this position must be BC/BE in Thoracic Surgery and should have demonstrated, by prior training and expertise, superior skills in all aspects of adult and pediatric cardiac surgery as well as general thoracic surgery. The physician will be responsible for the care of patients in an established cardiothoracic practice at The Hitchcock Clinic with privileges extended to the Veterans Administration Hospital in White River Junction, Vermont.

The successful candidate should have demonstrated a commitment to research by previous experience and publications and will have the opportunity for further academic pursuits, including the education and training of medical students and house staff physicians. The individual will be an employee of The Hitchcock Clinic and will receive an appropriate academic appointment as a member of the faculty of Dartmouth Medical School. DHMC is an AAEO employer and is especially interested in identifying female and minority candidates.

Inquiries and resumes should be directed to Charles A.S. Marrin, M.B., B.S., Chairman, Cardiothoracic Surgery Search Committee, Dartmouth-Hitchcock Medical Center, Lebanon, New Hampshire 03756, (603) 650-7390.



**Dartmouth-Hitchcock
Medical Center**

The Hitchcock Clinic
Lebanon, New Hampshire

CARDIAC SURGERY FELLOW

Crozer-Chester Medical Center has an expanding adult cardiac surgery program. We are located in the suburban Philadelphia area.

The position is available July 1, 1993, for a Cardiac Surgery Fellow. Board eligibility in thoracic surgery desirable. Experience in cardiac surgery and post-operative care required. Pennsylvania license needed.

Excellent pay package, benefits and working conditions in a pleasant environment.

Please contact: **Susan Ward, Crozer-Chester Medical Center, One Medical Center Boulevard, Upland, PA 19013-3395; Phone 215/447-2785.**

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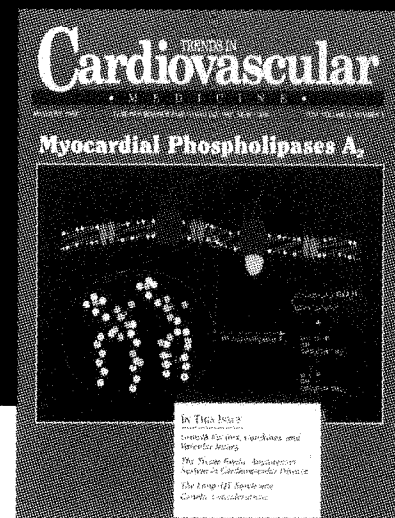
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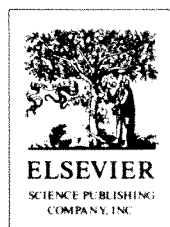
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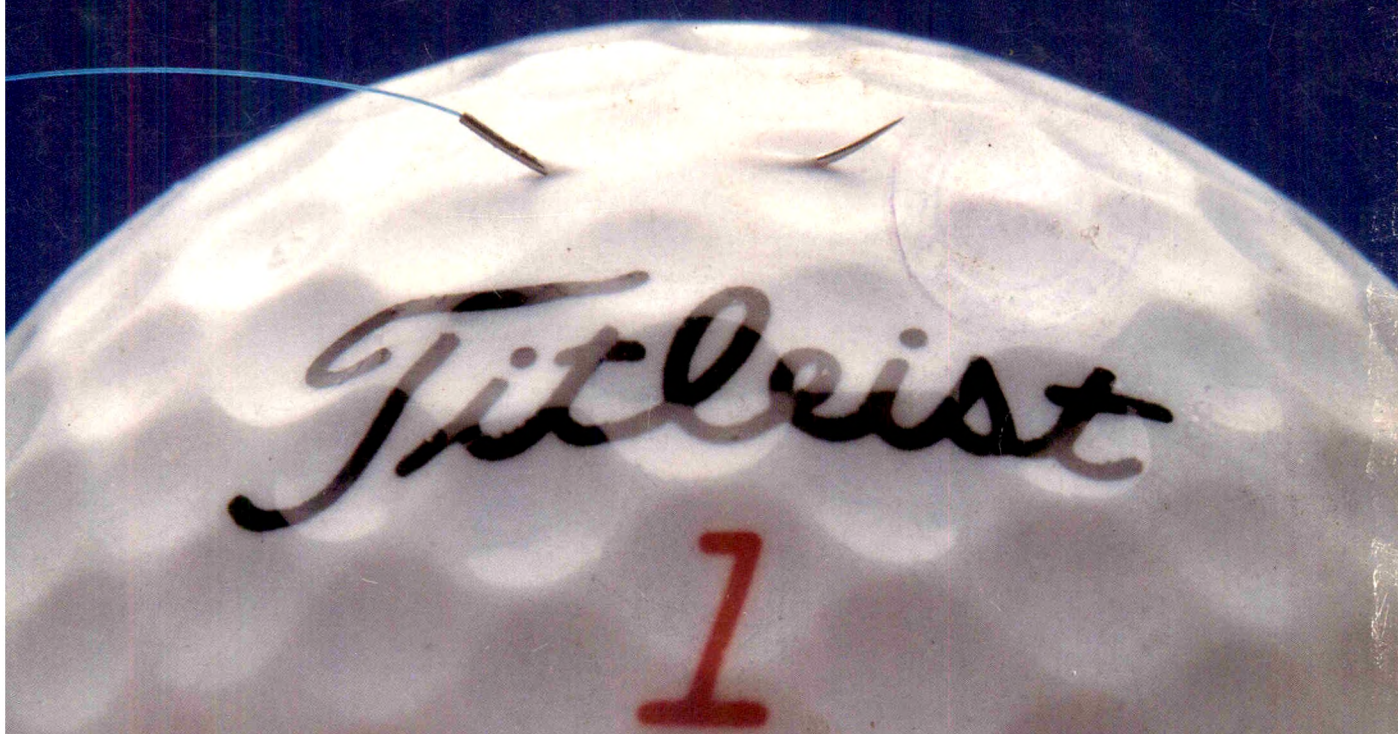
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